(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 534 443 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
30.12.1998 Bulletin 1998/53

(21) Application number: **92116413.3**

(22) Date of filing: **24.09.1992**

(51) Int Cl.[6]: **C07D 237/34**, C07D 403/04, C07D 409/04, C07D 409/14, C07D 407/04, C07D 407/14, C07D 417/04, C07D 417/14, C07D 401/14, C07D 401/04, C07D 413/04, C07D 413/14, C07D 409/12, C07D 495/04, C07D 491/04, A61K 31/50

(54) 3,6-Disubstituted pyridazine derivatives

3,6-disubstituierte Pyridazin-Derivate

Dérivés de la pyridazine 3,6-disubstituée

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(30) Priority: **26.09.1991 JP 247647/91**
18.12.1991 JP 335277/91
08.09.1992 JP 239545/92

(43) Date of publication of application:
31.03.1993 Bulletin 1993/13

(73) Proprietor: **Mitsubishi Chemical Corporation**
Chiyoda-ku Tokyo (JP)

(72) Inventors:
- **Iwase, Norimichi**
  Yokohama-shi, Kanagawa-ken (JP)
- **Morinaka, Yasuhiro**
  Tsutiura-shi, Ibaraki-ken (JP)
- **Tamao, Yoshikuni**
  Machida-shi, Tokyo (JP)
- **Kanayama, Toshiji**
  Yokohama-shi, Kanagawa-ken (JP)
- **Yamada, Kumi**
  Yamato-shi, Kanagawa-ken (JP)

(74) Representative:
TER MEER STEINMEISTER & PARTNER GbR
Mauerkircherstrasse 45
81679 München (DE)

(56) References cited:
EP-A- 0 159 652 **DE-A- 2 021 195**

- **PATENT ABSTRACTS OF JAPAN vol. 15, no. 293 (C-853)(4821) 25 July 1991 & JP-A-3 106 873 (MORISHITA PHARMACEUT. CO. LTD.)**
- **PATENT ABSTRACTS OF JAPAN vol. 5, no. 114 (C-64)(786) 23 July 1981 & JP-A-56 053 659 (MITSUBISHI YUKA YAKUHIN K. K.)**
- **PATENT ABSTRACTS OF JAPAN vol. 15, no. 293 (C-853)(4821) 25 July 1991 & JP-A-3 106 873 (MORISHITA PHARMACEUT. CO. LTD.)**
- **JOURNAL OF MEDICINAL CHEMISTRY vol. 12, no. 3, May 1969, WASHINGTON US pages 555 - 6 H.M. HOLAVA ET AL.**

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

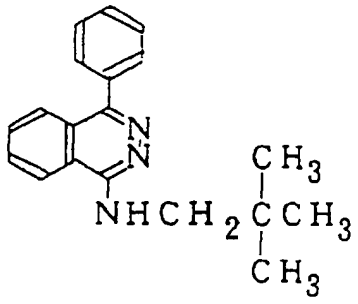
EP 0 534 443 B1

Description

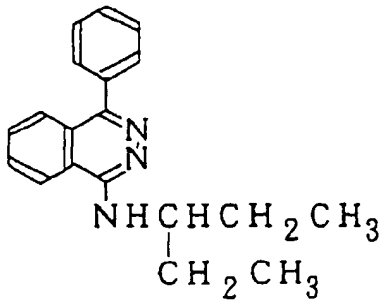
The present invention relates to 3,6-disubstituted pyridazine derivatives and, more particularly, to 3,6-disubstituted pyridazine derivatives which have platelet agglutination inhibitory action and, hence, are useful as a preventive medicine or a therapeutic medicine for a cerebrovascular disorder such as cerebral thrombosis and cerebral embolism, an ischemic heart disease such as myocardial infarction, and a circulation disorder such as a peripheral circulation disorder. The present invention also relates to optical antipodes of such 3,6-disubstituted pyridazine derivatives and pharmaceutically acceptable acid-addition salts thereof.

Most cerebrovascular disorders such as cerebral thrombosis and cerebral embolism, ischemic heart diseases such as myocardial infarction, and circulation disorders such as a peripheral circulation disorder are caused by a thrombus which is produced in a blood vessel and which occludes the blood vessel. Such a thrombus is produced mainly because platelets agglutinate in the earlier stage of the formation of the thrombus.

As compounds having a platelet agglutination inhibitory action, various 4-phenylphthalazine derivatives are conventionally known. For example, Japanese Patent Laid-Open Nos. 53659/1981, 53660/1981 and 48972/1982 disclose 1-anylino-4-phenylphthalazine derivatives, and Japanese Patent Laid-Open Nos. 218377/1985 and 243074/1985 disclose the compounds represented by the following general formulas (II) and (III), respectively, as compounds having a strong platelet agglutination inhibitory action in vitro:



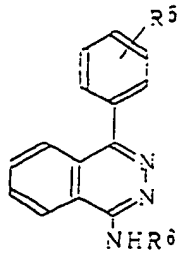
... (II)



... (III)

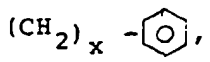
These compounds, however, show almost no platelet agglutination inhibitory action whey they are administered orally, or the platelet agglutination inhibitory action in vivo cannot be said to be satisfactory.

British Patent No. 1303016, Journal of Medicinal Chemistry, 12,555 (1969), etc. disclose 1-amino-4-phenylphthalazine derivatives represented by the following general formula (IV):



... (IV)

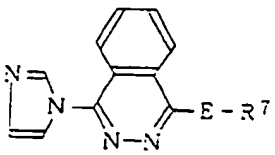
wherein R^5 represents a hydrogen atom or a chlorine atom, R^6 represents an alkyl group having 1 to 3 carbon atoms, $-(CH_2)_yN(CH_3)_2$, wherein y represents 2 or 3, a cyclohexyl group, or



wherein x represents 1 or 2.

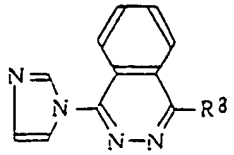
However, the compounds concretely disclosed have a restricted structure, and only an anti-inflammatory action and an anti-rheumatoid action are described as the pharmaceutical effects thereof.

As phthalazine derivatives having a non-substituted imidazole group at the fourth position, Japanese Patent Laid-Open Nos. 129180/1990, 129181/1990, 129182/1990 and 129183/1990 disclose compounds represented by the following general formulas (V) to (VIII), respectively:



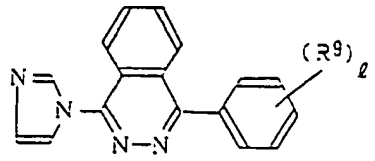
... (V)

wherein E represents -NH-, -O- or -S-, and R^7 represents a straight-chain or branched-chain alkyl group having 1 to 18 carbon atoms, a straight-chain or branched-chain alkyl group having 2 to 4 carbon atoms containing a hydroxyl group, an allyl group, a 3-methoxypropyl group, a tetrahydrofurfuryl group, a furfuryl group, a benzyl group which may be substituted by a chlorine atom or an alkyl group, or a phenyl group which may be substituted by a phenethyl group, a pyridylmethyl group or a chlorine atom, provided that when E is -NH-, R^7 is not a substituted or non-substituted phenyl group;



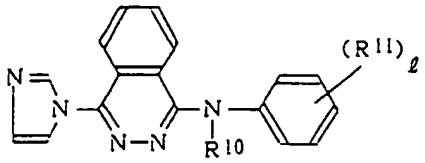
... (VI)

wherein R^8 represents a lower alkoxyphenyl group, an allyloxyphenyl group, a pyridylmethyloxyphenyl group, a furyl group which may have a substituent, a thienyl group which may have a substituent, or a naphthyl group which may have a substituent;



... (VII)

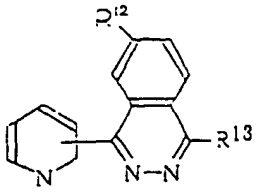
wherein R^9 which may be the same or different from each other represents a hydroxyl group, a lower alkyl group, a methoxy group, an acetylamino group, a halogen atom, a methylthio group or an ethoxycarbonylvinyl group, and ℓ represents an integer of 0 to 3; and



... (VIII)

wherein R^{10} represents a hydrogen atom, a lower alkyl group, R^{11} which may be the same or different from each other represents a hydroxyl group, an alkyl group having 1 to 5 carbon atoms, a lower alkoxy group, an acylamino group, a halogen atom, a cyano group, a nitro group, an anmino group, a carboxyl group, a lower alkoxycarbonyl group, a lower alkylcarbonyl group or an alkylthio group, and ℓ represents an integer of 0 to 3.

As a phthalazine derivative having a non-substituted pyridyl group at the fourth position, Japanese Patent Laid-Open No. 106873/1991 discloses a compound represented by the following general formulas (IX):

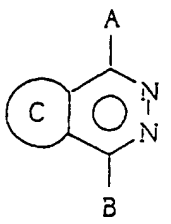


... (IX)

wherein R^{12} represents a hydrogen atom or a methoxy group, and R^{13} represents $-NR^{14}R^{15}$, wherein R^{14} represents an alkyl group, a phenyl group which may be substituted by a halogen atom or a cyano group, or a pyrimidinyl group which may have a substituent, and R^{15} represents a hydrogen atom or a lower alkyl group, or R^{14} and R^{15} may combine to form a piperidino group, a piperazino group, a morpholino group or an imidazolyl group.

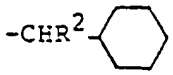
As a result of studies of pyridazine derivatives having excellent platelet agglutination inhibitory action, the present inventors have found that 3,6-disubstituted pyridazine derivatives satisfy the above-desribed requirements. The present invention has been achieved on the basis of this finding.

The present invention provides 3,6-disubstituted pyridazine derivatives represented by the following general formula (I), optical antipodes thereof and pharmaceutically acceptable acid-addition salts thereof:



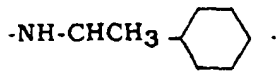
... (I)

wherein A represents a phenyl group, a thienyl group or a furyl group, each of which may be substituted by an alkyl group having 1 to 4 carbon atoms; B represents -NH-D [wherein D represents



(wherein R_2 represents an alkyl group having 1 to 4 carbon atoms)]; and the ring C represents a benzene ring; a furan ring; or a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms.

In a preferred embodiment, A represents a phenyl group and B represents



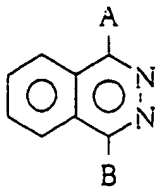
.

The present invention also provides a pharmaceutical composition containing, as an active ingredient, a 3,6-disubstituted pyridazine derivative ofthe above formula (I), an optical antipode thereof and a salt thereof.

The present invention also provides a process for the preparation of a 3,6-disubstituted pyridazine derivative of the above formula (I), an optical antipode thereof or a salt thereof.

Concrete Examples of the compounds according to the present invention will be shown in Tables 1 to 5.

Table 1



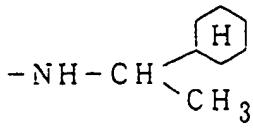
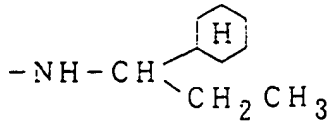
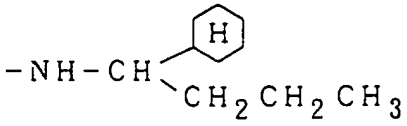
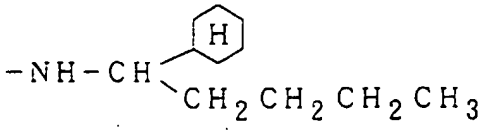
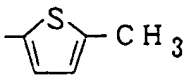
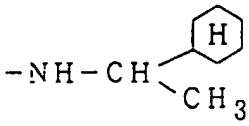
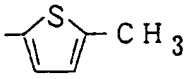
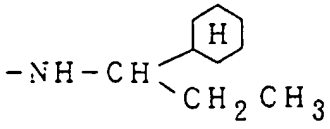
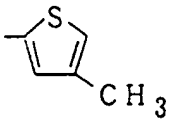
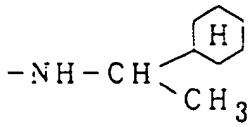
Comp. No.	A	B
1		
2		
3		
4		
5		
6		
7		

Table 1 (continued)

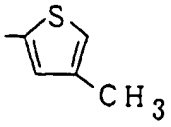
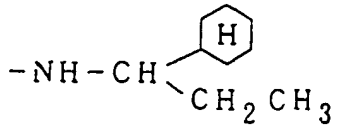
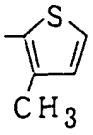
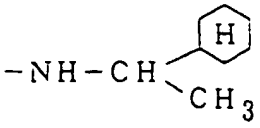
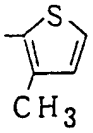
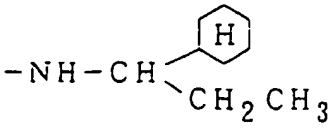
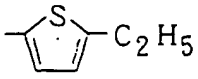
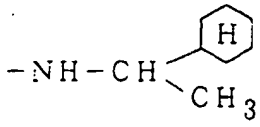
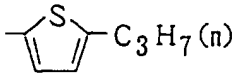
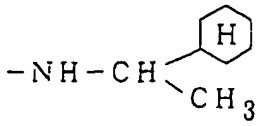
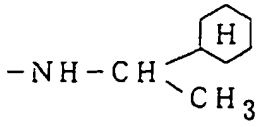
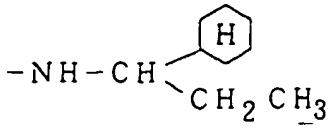
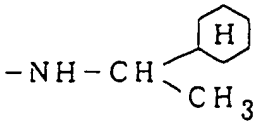
Comp. No.	A	B
8		
9		
10		
11		
12		
13		
14		
15		

Table 1 (continued)

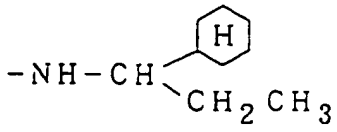
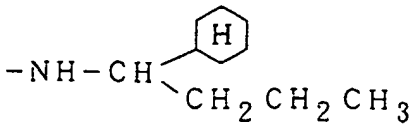
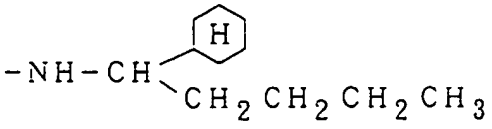
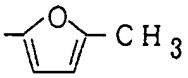
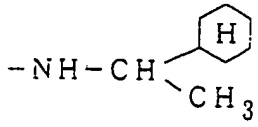
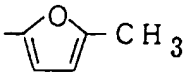
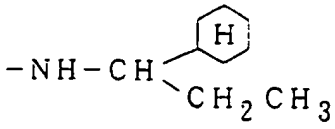
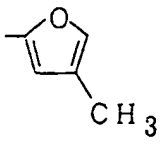
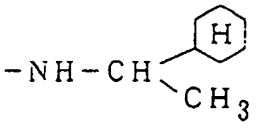
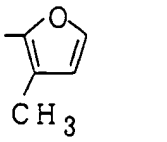
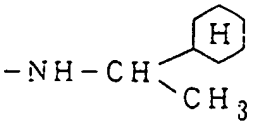
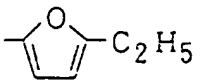
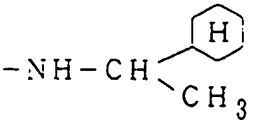
Comp. No	A	B
16		
17		
18		
19		
20		
21		
22		
23		

Table 1 (continued)

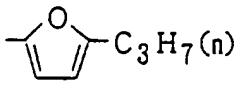
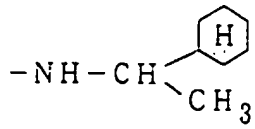
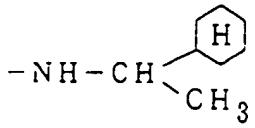
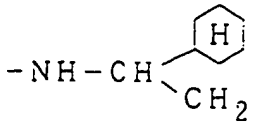
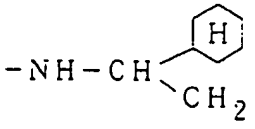
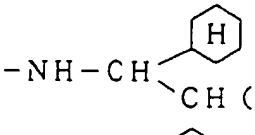
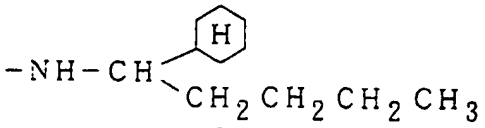
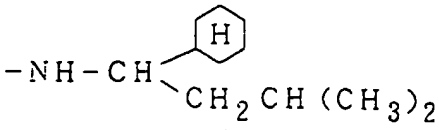
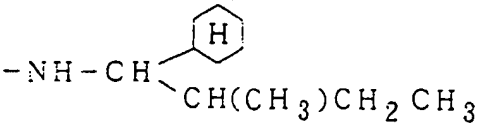
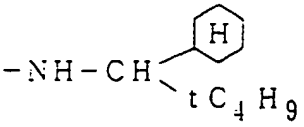
Comp. No.	A	B
24		
25		
26		
27		
28		
29		
30		
31		
32		

Table 1 (continued)

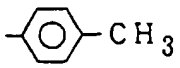
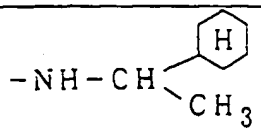
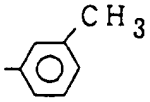
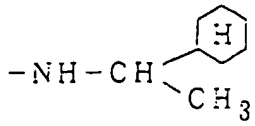
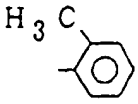
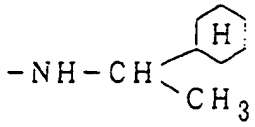
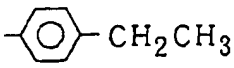
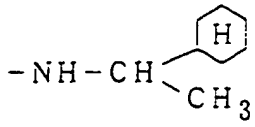
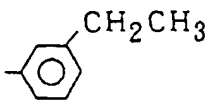
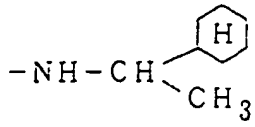
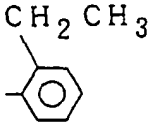
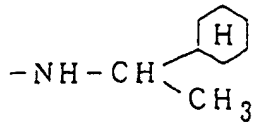
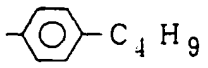
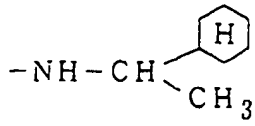
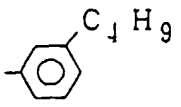
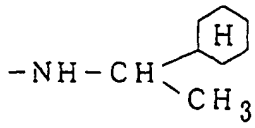
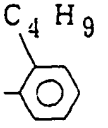
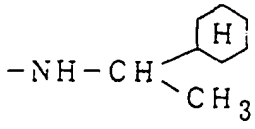
Comp. No.	A	B
33		
34		
35		
36		
37		
38		
39		
40		
41		

Table 1

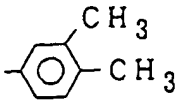
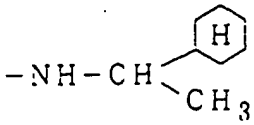
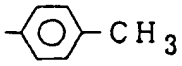
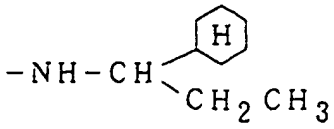
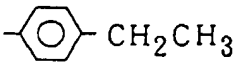
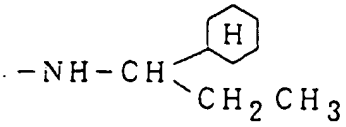
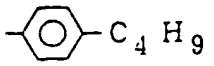
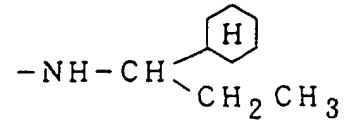
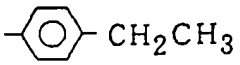
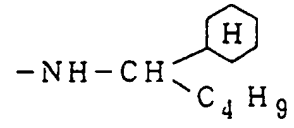
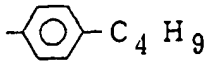
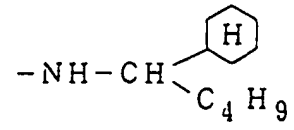
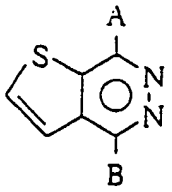
Comp. No.	A	B
42		
43		
44		
45		
46		
47		

Table 2



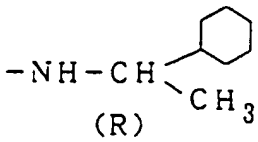
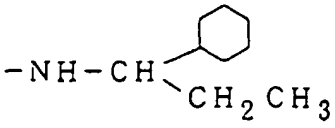
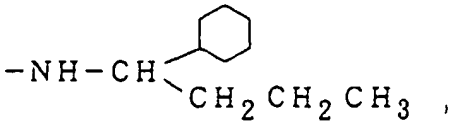
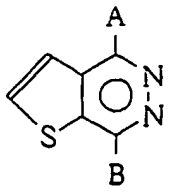
Comp. No.	A	B
48		 (R)
49		
50		

Table 3



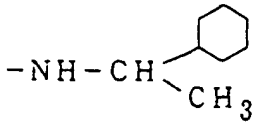
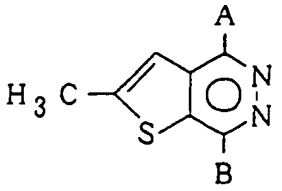
Comp. No.	A	B
51		

Table 4



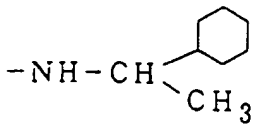
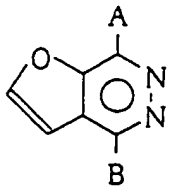
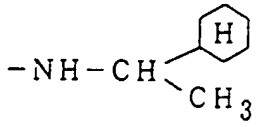
Comp. No.	A	B
52		

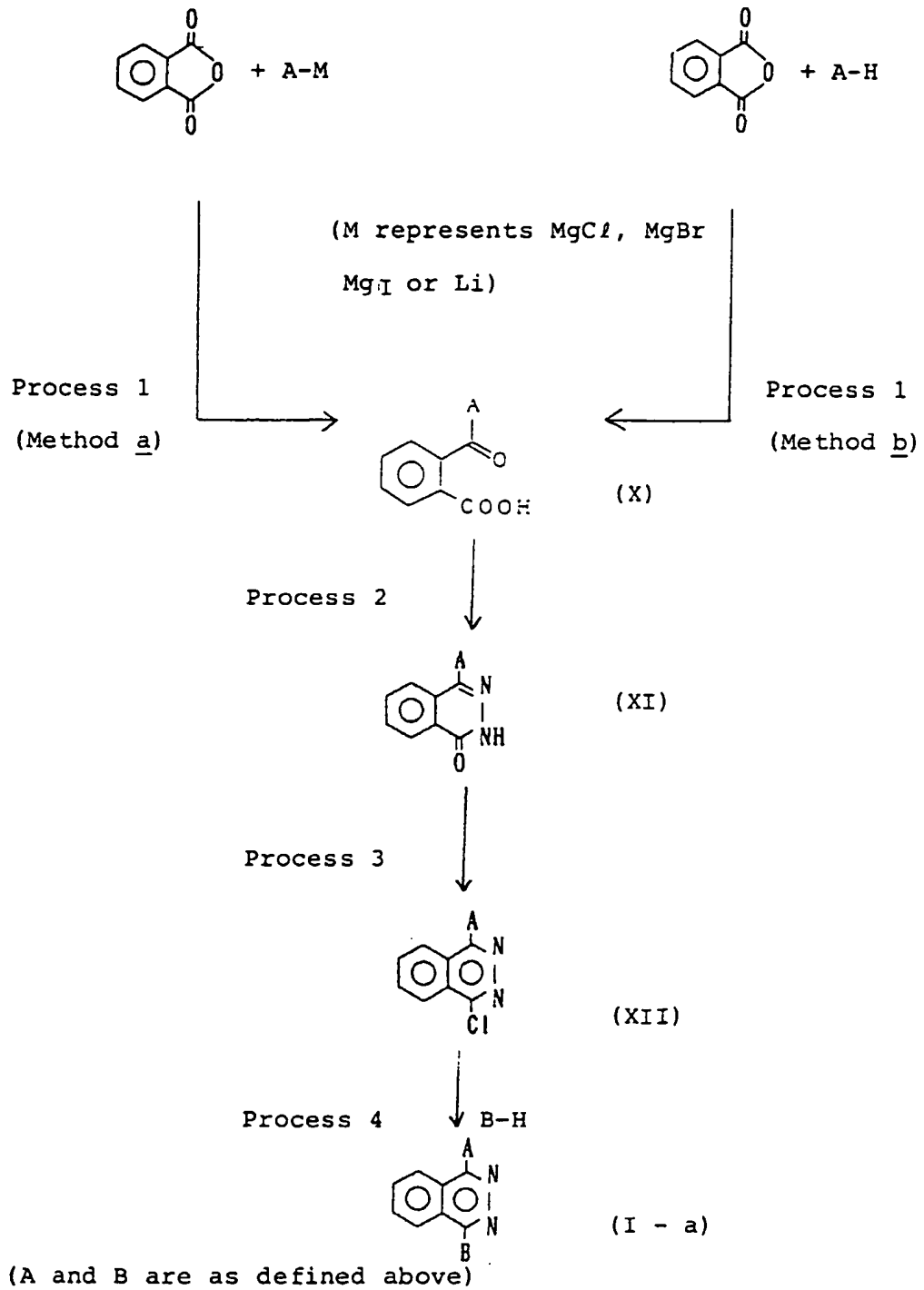
Table 5



Comp. No.	A	B
53		

A process for preparing a compound according to the present invention will now be explained. A compound according to the present invention can be synthesized by a given method which meets the object of the present invention including the following methods.

(i) When the ring C represents a benzene ring,



The process 1 is a process for preparing a compound (X). The compound (X) can be prepared either by a method a or a method b. The method a is a method of preparing the compound (X) by reacting phthalic anhydride with Grignard reagent or lithium reagent. In the case of using a solvent, ether, tetrahydrofuran, dioxane, benzene, toluene, methylene chloride, dichloroethane, dimethylformamide, N-methylpyrrolidone, hexamethylphosphoroamide or the like is used either singly or in the form of a mixture. The reaction temperature is -78 to 100°C, preferably -78 to 30°C, and the reaction time is 10 minutes to 24 hours.

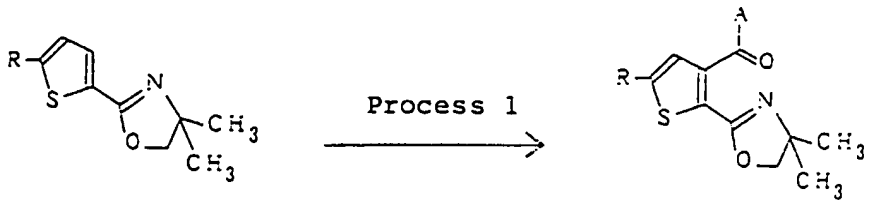
The method b is a method of preparing the compound (X) by a Friedel-Crafts reaction between phthalic anhydride and a compound represented by the formula A-H, wherein A is as defined above. In the case of using a catalyst, aluminum chloride, titanium tetrachloride, tin chloride, boron trifluoride etherate or the like is used. In the case of using a solvent, methylene chloride, dichloroethane, nitrobenzene, carbon disulfide or the like is used. The reaction temperature is -78 to 200°C, preferably -50 to 100°C, and the reaction time is 10 minutes to 24 hours.

The process 2 is a process for preparing a compound (XI). By reacting the compound (X) and hydrazine or hydrazine hydrate, the compound (XI) is prepared. In the case of using a solvent, water, methanol, ethanol, benzene, toluene or the like is used. The reaction temperature is 0 to 150°C, preferably 20 to 100°C.

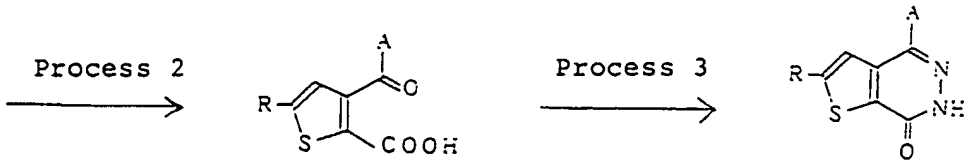
The process 3 is a process for preparing a compound (XII) by a chlorination of the compound (XI) without a solvent or in a solvent such as benzene, toluene, chloroform and dichloroethane. As a chlorinating agent, thionyl chloride, phosphorus oxychloride, phosphorus trichloride, phosphorus pentachloride or the like is used.

The process 4 is a process for preparing a compound (I - a) according to the present invention from the compound (XII). The compound (XII) is reacted with a compound represented by the formula B-H, wherein B represents the same as defined above. Examples of solvents used are ethers such as tetrahydrofuran and dioxane; hydrocarbon halides such as chloroform and dichloroethane; aromatic hydrocarbons such as benzene, toluene, xylene and chlorobenzene; amides such as dimethylformamide and N-methylpyrrolidone; and dimethylsulfoxide. The amount of solvent used is 0.1 to 100 by weight ratio based on the compound (XII). In the case of using a catalyst, an organic base such as triethylamine, disopropylethylamine, pyridine and N,N-dimethylanyline, or an inorganic base such as NaOH, KOH, $NaHCO_3$, Na_2CO_3, $KHCO_3$ and K_2CO_3 is used. The amount of catalyst used is 0.5 to 30, preferably 1 to 10 by weight ratio based on the compound (XII). The reaction temperature is 0 to 300°C, preferably 20 to 150°C, and the reaction time is 10 minutes to 24 hours.

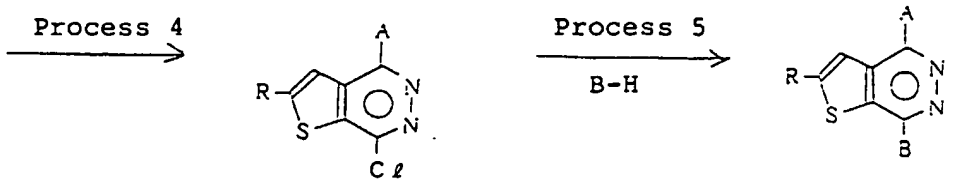
(ii) When the ring C represents a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms,



(XIII) (XIV)



(XV) (XVI)



(XVII) (I - b)

wherein A and B are as defined above and R represents an alkyl group having 1 to 4 carbon atoms.

The process 1 is a process for introducing

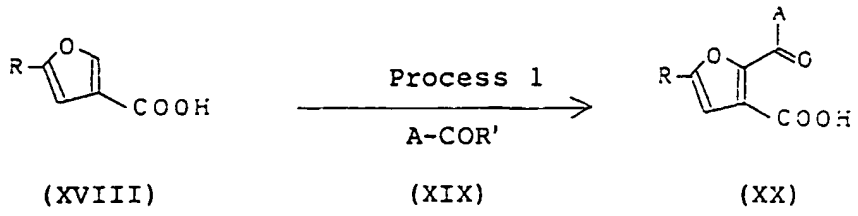
group into the ortho position of a compound (XIII) so as to prepare a compound (XIV). A base such as butyl lithium is brought into reaction with the compound (XIII) so as to produce an ortho-lithiated compound. A compound represented by the general formula A-COR' (wherein A is as defined above, and R' represents a halogen atom, an alkoxy group, an imidazolyl group or a cyano group) is then reacted with the thus-produced ortho-lithiated compound, thereby preparing the compound (XIV). In the case of using a solvent, ether, tetrahydrofuran, etc. are used either singly or in the form of a mixture.

The process 2 is a process for cleaving the oxazoline ring of the compound (XIV) so as to prepare a compound (XV). The reaction is carried out in the presence of an acid such as hydrochloric acid, sulfuric acid, mesylic acid and tosylic acid. As a solvent, water, dioxane, tetrahydrofuran, ethanol, methanol, etc. are used either singly or in

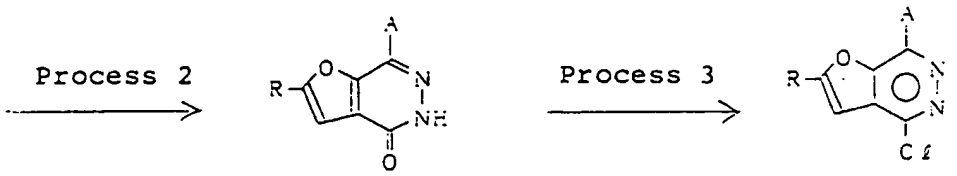
the form of a mixture.

The processes 3, 4 and 5 correspond to the processes 2, 3 and 4, respectively, in (i) when the ring C represents a benzene ring.

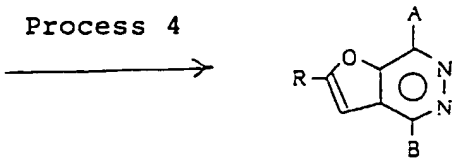
(iii) When the ring C represents a furan ring which may be substituted by an alkyl group having 1 to 4 carbon atoms,



(XVIII) (XIX) (XX)



(XXI) (XXII)



(I - c)

wherein A and B are as defined above and R represents an alkyl group having 1 to 4 carbon atoms.

The process 1 is a process for introducing A-C=O group into the second position of a compound (XVIII) so as to prepare a compound (XX). The reaction is carried out by bringing the dilithiated compound of the compound (XVIII) which is produced by a base into reaction with a compound represented by the general formula A-COR' (wherein A is as defined above, and R'represents a halogen atom, an alkoxy group, an aryloxy group, an imidazolyl group or a cyano group). At this time, n-butyllithium, s-butyllithium, LDA, LHMDS, etc. are usable as a base. The amount of base used is 1 to 10, preferably 2 to 4 by molar ratio. As a solvent, tetrahydrofuran, diethyl ether, diisopropyl ether, hexane, heptane, etc. are used either singly or in the form of a mixture.

The processes 2, 3, and 4 correspond to the processes 2, 3 and 4, respectively, in (i) when the ring C represents a benzene ring.

The salts of the compound represented by the general formula (I) are preferably physiologically tolerable salts.

They are, for example, the salts of inorganic acids such as hydrochlorides, hydrobromides, hydroiodides, sulfides and phosphates, and the salts of organic acids such as methane sulfonates, p-toluene sulfonates, benzene sulfonates, camphor sulfonates, acetates, benzoates, malates, lactates, glycolates, glucronates, maleates, fumarates, oxalates, ascorbates, citrates, salicylates, nicotinates and tartrates. Since some compounds represented by the general formula (I) and some salts thereof exist in the form of a hydrate or a solvate, the compounds of the present invention include the hydrates and solvates thereof.

When a compound of the present invention is orally administered to an adult as a medicine, it is preferable that a dose of 1 to 100 mg is administered 1 to 3 times a day. In the case of using a compound of the present invention as an intravenous injection for an adult, it is preferable that a dose of 0.01 to 10 mg is administered 2 to 5 times a day. In the case of using a compound of the present invention as a medicine for intestinal administration for an adult, it is preferable that a dose of 1 to 100 mg is administered 1 to 3 times a day. It is more preferable to appropriately increase or decrease the dose depending upon the age, the condition of the disease and the condition of the patient.

When a compound of the present invention is formed into a medicine, at least one compound represented by the general formula (I) or at least one pharmaceutically tolerable salt thereof is mixed with a pharmaceutical carrier, a shaping agent and other additives. The carrier may be either a solid or a liquid. Examples of a solid carrier are lactose, white clay (kaolin), sucrose, crystalline cellulose, cornstarch, talc, agar agar, pectin, acacia gum, stearic acid, magnesium stearate, lecithin and sodium chloride.

Examples of a liquid carrier are syrup, glycerin, peanut oil, polyvinyl pyrrolidone, olive oil, ethanol, benzyl alcohol, propylene glycol, and water.

Such a medicine may be used in various forms. In the case of using a solid carrier, a medicine may be prepared in the form of tablets, powder, hard gelatin capsules, suppositories or troche. The amount of solid carrier may be varied in a wide range, but it is preferably about 1 mg to 1 g.

In the case of using a liquid carrier, a medicine may be prepared in the form of syrup, emulsion, soft gelatin capsule, sterile injection contained in an ampule or the like, or aqueous or nonaqueous suspension.

The present invention will be explained in more detail hereinunder with reference to the following examples. It is however, to be understood that the present invention is not restricted thereto and any modification is possible within the scope of the present invention.

[Examples]

Reference Example 1

Synthesis of (R)-1-(α-phenylethylamino)-4-cyclohexylphthalazine

10.0 g of phthalic anhydride was dissolved in 200 mℓ of tetrahydrofuran, and 40 mℓ of cyclohexylmagnesium chloride (2.0 M, ether solution) was added dropwise to the solution at -50°C. After stirring the solution at the same temperature for 1 hour, the reaction solution was poured into 0.5-N hydrochloric acid, and extracted with chloroform. After the organic layer was dried over magnesium sulfide, it was purified by silica gel chromatography (eluent: chloroformmethanol) to obtain 12.0 g of o-(cyclohexanoyl) benzoic acid.

12.0 g of o-(cyclohexanoyl) benzoic acid and 3.1 g of hydrazine hydrate were dissolved in 60 mℓ of ethanol, and the solution was refluxed for 4 hours. Ethanol was distilled off and the remaining solution was crystallized by adding ether, thereby obtaining 7.5 g of 4-cyclohexyl-1-phthalazinone.

1.0 g of 4-cyclohexyl-1-phthalazinone and 5 mℓ of phosphorus oxychloride were dissolved in 10 mℓ of dichloroethane, and the solution was stirred at 100°C for 4 hours. The reaction solution was distilled off, and a 1-N aqueous NaOH solution was added thereto under cooling with ice. The solution was extracted with chloroform and dried over magnesium sulfide. The solvent was then distilled off, thereby obtaining 1.1g of 1-chloro-4-cyclo-hexylphthalazine.

1.1g of 1-chloro-4-cyclohexylphthalazine and 1.6 g of D-α-phenylethylamine were dissolved in N-methylpyrrolidone, and the solution was stirred at 140°C for 6 hours. After cooling the solution, an aqueous 5% NaOH solution was added to the solution, and the resultant solution was extracted with chloroform. The organic layer was dried, concentrated, purified by silica gel chromatography (eluent: hexane, chloroform, ethyl acetate), and recrystallized from ether to obtain 1.05 g of (R)-1-(α-phenylethylamino)-4-cyclohexylphthalazine.

Melting point: 162.5 to 164.0°C.

Examples 1 and 2

Compounds of Examples 1 and 2 shown in Table 6 were synthesized in accordance with the method in Reference Example 1.

Example 3

Synthesis of (R)-1-(α-cyclohexylethylamino)-4-(2-furyl) phthalazine (Compound No. 15 in Table 1)

3.4 g of furan was dissolved in 30 mℓ of tetrahydrofuran, and the solution was added dropwise to 34 mℓ of normal butyllithium (1.6 M, hexane solution) at -40°C. After stirring the resultant solution at 0°C for 4 hours, the lithium reagent was added dropwise to a solution of 7.4 g of phthalic anhydride in 100 mℓ of tetrahydrofuran at -70°C. After stirring the solution at the same temperature for 1 hour, the reaction solution was poured into 0.5-N hydrochloric acid, and extracted with chloroform. By purification by column chromatography (eluent: chloroform, methanol), 2.0 g of o-(2-furoyl) benzoic acid was obtained.

2.0 g of o-(2-furoyl) benzoic acid and 690 mg of hydrazine hydrate were dissolved in 30 mℓ of ethanol, and the solution was refluxed for 4 hours.

After cooling the solution, it was crystallized by adding ether, thereby obtaining 1.0 g of 4-(2-furyl)-1-phthalazinone.

1.0 g of 4-(2-furyl)-1-phthalazinone and 5 mℓ of phosphorus oxychloride were dissolved in 5 mℓ of dichloroethane, and the solution was stirred at 100°C for 3 hours. The reaction solution was distilled off, and a 1-N aqueous NaOH solution was added thereto under cooling with ice. The solution was extracted with chloroform, dried and concentrated to obtain 910 mg of 1-chloro-4-(2-furyl)phthalazine.

300 mg of 1-chloro-4-(2-furyl)phthalazine and 495 mg of R-cyclohexylethylamine were dissolved in 2 mℓ of N-methylpyrrolidone, and the solution was stirred at 150°C for 8 hours. After the solution was subjected to after-treatment, it was purified by column chromatography, thereby obtaining 135 mg of (R)-1-(α-cyclohexylethylamino)-4-(3-furyl) phthalazine.

Melting point: 152.0 to 153.0°C.

Reference Example 2

Synthesis of 1-(1-imidazolyl)-4-(2-furyl)phthalazine

300 mg of 1-chloro-4-(2-furyl)phthalazine and 707 mg of imidazol were dissolved in 2 mℓ of N-methylpyrrolidone, and the solution was stirred at 150°C for 10 hours. After the solution was subjected to after-treatment, it was purified by column chromatography, thereby obtaining 14.5 mg of 1-(1-imidazolyl)-4-(2-furyl)phthalazine.

Melting point: 151.0 to 152.5°C.

Example 4

Compound of Example 4 shown in Table 6 was synthesized in accordance with the method in Reference Example 2.

Example 5

Synthesis of (R)-1-(1-cyclohexylethylamino)-4-phenylphthalazine (R compound of Compound No. 25 in Table 1)

722 mg (3.0 mmol) of 1-chloro-4-phenylphthalazine and 1.15 g (9.0 mmol) of (R)-(-)-1-cyclohexylethylamine were added to 2 mℓ of N-methylpyrrolidone, and the resultant mixture was stirred at 120 to 130°C for 6 hours under heating. After the end of the reaction, the mixture was cooled. 20 mℓ of an aqueous 5% NaOH solution was added to the mixture and the solution was extracted with chloroform. The organic layer was dried over $MgSO_4$, concentrated, purified by silica gel chromatography (eluent: ethyl acetate : hexane : chloroform = 1 : 3 : 1) and recrystallized from ether-chloroform, thereby obtaining 751 mg of (R)-1-(1-cyclohexylethylamino)-4-phenylphthalazine.

Melting point: 164.0 to 167.0°C.

Examples 6 to 10

Compounds of Examples 6 to 10 shown in Table 6 were synthesized in accordance with the method in Example 5.

Table 6

Comp. of Ex. No. (Comp. No. in Table1)	m.p. (°C)
1 (No. 1)	88.0~92.0

Table 6 (continued)

Comp. of Ex. No. (Comp. No. in Table1)	m.p. (°C)
2 (No. 2)	amorphous
4 (No. 19)	168~175 decomposition
6 (No. 25)	165.0~167.0
7 (No. 26)	amorphous
8 (No. 27)	139.0~145.0
9 (No. 28)	147.0~150.0
10 (No.35)	amorphous

In Table 6, the compounds in Examples 1 and 10 are R compounds, the compound in Example 6 is an S compound, and the compounds in Examples 7, 8 and 9 are RS compounds. The compound in Example 4 is a fumarate.

Reference Example 3

Synthesis of (R)-4-(1-phenylethylamino)-7-(2-thienyl)-thieno[2.3-d]pyridazine

2.0 g of 2-(3-thienyl)-4,4-dimethyloxazoline was dissolved in 50 ml of ether, and 10 ml of s-butyllithium (1.3 M, cyclohexane solution) was added dropwise thereto at -70°C. The solution was stirred for 1 hour. The reaction solution was added dropwise to a solution of 2.4 g of 2-thenoyl chloride in 50 ml of tetrahydrofuran at -78°C, and the solution was stirred for 30 minutes. Thereafter, 1 mℓ of methanol was added to the solution, and the reaction solution was concentrated. After adding water thereto, the solution was extracted with chloroform. The chloroform layer was dried and concentrated, and the residue was purified by silica gel chromatography to obtain 2.8 g of 2-(2-thenoyl)-3-(4,4-dimethyl-2-oxazoline-2-yl)thiophene.

2.8 g of 2-(2-thenoyl)-3-(4,4-dimethyl-2-oxazoline-2-yl)thiophene was added to a solution of 30 mℓ of concentrated hydrochloric acid, 20 mℓ of water and 20 mℓ of dioxane, and the solution was stirred at 100°C for 8 hours. After cooling the solution, an aqueous NaCℓ solution was added thereto. The resultant solution was extracted with chloroform and dried. After the solvent was distilled off, the residue was purified by silica gel chromatography to obtain 0.70 g of 2-(2-thenoyl)-3-thiophene carboxylic acid.

0.70 g of 2-(2-thenoyl)-3-thiophene carboxylic acid and 0.22 g of hydrazine hydrate were dissolved in 20 mℓ of ethanol, and the solution was refluxed for 5 hours. After cooling the solution, it was crystallized by adding ether, thereby obtaining 0.61 g of 7-(2-thienyl)thieno[2,3-d]-pyridazine-4(5H)-one.

0.30 g of 7-(2-thienyl)thieno[2,3-d]pyridazine-4(5H)-one and 0.30 g of phosphorus oxychloride were dissolved in 10 mℓ of dichloroethane, and the solution was stirred at 100°C for 10 hours. The reaction solution was concentrated, and a 1-N aqueous KOH solution was added thereto under cooling with ice. The solution was extracted with chloroform and dried. The solvent was distilled off, thereby obtaining 0.31 g of 4-chloro-7-(2-thienyl)thieno[2,3-d]pyridazine.

0.31 g of 4-chloro-7-(2-thienyl)thieno[2,3-d]pyridazine and 0.48 g of (R)-1-phenylethylamine was dissolved in 2 mℓ of N-methylpyrrolidone, and the solution was stirred at 150°C for 10 hours. After cooling the solution, an aqueous 5% KOH solution was added thereto, and the solution was extracted with chloroform and dried. The solvent was distilled off, and the residue was purified by silica gel chromatography to obtain 0.27 g of (R)-4-(1-phenylethylamino)-7-(2-thienyl)-thieno[2,3-d]pyridazine.

Melting point: 215.5 to 216.5°C.

Examples 11 to 15

Compounds of Examples 11 to 15 shown in Tables 7, 8 and 9 were synthesized in accordance with the method in Reference Example 3.

Table 7

Comp. of Ex. No. (Comp No. in Table 2)	m.p. (°C)
11 (No. 48)	165.0~166.0
12 (No. 49)	amorphous
13 (No. 50)	amorphous

Table 8

Comp. of Ex. No. (Comp No. in Table 3)	m.p. (°C)
14 (No. 51)	amorphous

In Tables 7 and 8, the compounds in Examples 11 and 14 are R compounds.

Table 9

Comp. of Ex. No. (Comp. No. in Table 4)	m.p. (°C)
15 (No. 5 2)	152 ~154

In Table 9, the compound in Example 15 is an are R compound.

Example 16

Synthesis of (R)-4-(1-cyclohexylethylamino)-7-phenyl-furano[2,3-d]pyridazine (Compound No. 53 in Table 5)

5.96 g of diisopropylamine was dissolved in 50 mℓ of tetrahydrofuran, and 35 mℓ of n-butyllithium (1.6 M) was added dropwise thereto at 0°C, and then a solution of 3.0 g of 3-furoic acid in 20 mℓ of tetrahydrofuran was added dropwise thereto at -78°C. The reaction solution was added dropwise to a solution of 5.6 g of benzoyl chloride in 50 mℓ of tetrahydrofuran at -78°C, and the resultant solution was stirred for 30 minutes. After diluted hydrochloric acid was added, the mixed solution was extracted with chloroform and the extract was purified by silica gel chromatography to obtain 3.2 g of 2-benzoyl-3-froic acid.

3.0 g of 2-benzoyl-3-froic acid and 0.76 g of hydrazine hydrate were dissolved in 30 mℓ of ethanol, and the solution was refluxed for 3 hours. After cooling the solution, it was concentrated, and the residue was purified by silica gel chromatography to obtain 0.25 g of 7-phenyl-furano[2,3-d]pyridazine-4-(5H)-one.

0.15 g of 7-phenyl-furano[2,3-d]pyridazine-4-(5H)-one and 10 mℓ of phosphorus oxychloride were dissolved in 10 mℓ of dichloroethane, and the solution was stirred at 100°C for 3 hours. The reaction solution was concentrated, and a 1-N aqueous KOH solution was added thereto under cooling with ice. The solution was extracted with chloroform and dried. The solvent was distilled off, thereby obtaining 0.10 g of 4-chloro-7-phenyl-furano[2,3-d]pyridazine.

0.10 g of 4-chloro-7-phenyl-furano[2,3-d]pyridazine and 0.165 g of (R)-1-cyclohexylethylamine was dissolved in 1 mℓ of N-methylpyrrolidone, and the solution was stirred at 140°C for 6 hours. After cooling the solution, an aqueous 5% KOH solution was added thereto, and the solution was extracted with chloroform. By purifying the extract by silica gel chromatography, 0.061 g of (R)-4-(1-cyclohexylethylamino)-7-phenyl-furano[2,3-d]pyridazine was obtained.

Melting point: 126 to 130°C.

Experiment 1

Inhibitory effects of 3,6-disubstituted pyridazine derivatives on platelet agglutination of rats ex vitro

Arterial blood of a rat was centrifuged to obtain platelet rich plasma. 5 mℓ of a medicinal solution was added to 250 μℓ of the platelet rich plasma, and the mixture was incubated for 2 minutes. Thereafter, 3 μg of collagen (produced by Hormon-Chemie) was added to the mixture as a platelet agglutination inducer, and changes in the platelet agglutination were observed and recorded by a 2-channel platelet agglutination degree measuring instrument (Model DP247E, produced by Sienco) for 10 minutes.

The platelet agglutination inhibitory ratio was calculated from the following formula:

$$\text{Inhibitory ratio} = (Tc - Ts)/Tc \times 100$$

Tc: Agglutination degree when only a solvent was added
Ts: Agglutination degree when a medicinal solution was added

The inhibitory ratios of each compound having different mol concentrations are shown in Tables 10 to 13.

Experiment 2

Inhibitory effects of 3,6-disubstituted pyridazine derivatives on platelet agglutination of rats in vivo (oral administration)

A rat group consisting of 8 male Wistar-ST rats each weighing about 250 g was tested. Each compound was suspended in aqueous 1% tragacanth solution. The thus-prepared suspension was orally administered to each rat at a dose of 4 mℓ/kg. One hour after, blood was collected from each carotid artery through a cannula into a plastic test tube containing 3.8% sodium citrate in amount corresponding to 1/10 of the volume of the test tube) and the mixture was stirred. Thereafter, the mixture was centrifuged at 200 × g rpm for 15 minutes, and the supernatant liquid was taken as platelet rich plasma (PRP). The residue was further centrifuged at 2000 × g rpm for 15 minutes, and the supernatant liquid was collected as platelet poor plasma (PPP) and used for measurement of the platelet agglutinating ability. The platelet agglutinating ability was measured by a 2-channel platelet agglutination degree measuring instrument (Model DP247E, produced by Sienco), and recorded by a 2-pen recorder.

Collagen (produced by Hormon-Chemie) having a concentration of 7 to 10 μg/mℓ was used as a platelet agglutination inducer.

The platelet agglutination inhibitory ratio was calculated from the following formula:

$$\text{Inhibitory ratio} = (A - B)/A \times 100\ (\%)$$

A: Agglutination degree in the group (controlled group) to which only a solution of 1% tragacanth was administered
B: Agglutination degree in the group to which the tragacanth solution containing a compound was administered

The results are shown in Tables 10 to 13.

Table 10

Comp. of Ex. No. (Comp. No. in Table1)	in vitro Inhibitory ratio (%)			ex vivo Inhibitory ratio (%) (p.o)
	10^{-7}M	3 x 10^{-7}M	10^{-6}M	1mg/kg
1 (No. 1)	98.6			
2 (No. 2)	47.6	97.7		
3 (No. 15)	98.6			
5 (No. 25) (R)	94.3			51.3
6 (No. 25) (S)	30.2	94.4		

Table 10 (continued)

Comp. of Ex. No. (Comp. No. in Table1)	in vitro Inhibitory ratio (%)			ex vivo Inhibitory ratio (%) (p.o)
	10^{-7}M	3 x 10^{-7}M	10^{-6}M	1mg/kg
7 (No. 26)		61.3	83.5	
8 (No. 27)		90.3		
10 (No. 35)	93.2			

In Table 10, the compounds in Examples 1, 3, 5 and 10 are R compounds, the compound in Example 6 is an S compound, and the compounds in Examples 7 and 8 are RS compounds.

Table 11

Comp. of Ex. No. (Comp. No. in Table 2)	in vitro Inhibitory ratio(%)			ex vivo Inhibitory ratio (%)(p. o)
	10^{-7}M	3 x 10^{-7}M	10^{-6}M	1 mg/kg
11 (No. 48)	94.6			50.2

In Table 11, the compound in Example 11 is a R compound.

Table 12

Comp. of Ex. No. (Comp. No. in Table 3)	in vitro Inhibitory ratio(%)			ex vivo Inhibitory ratio (%)(p. o)
	1 0^{-7}M	3 x 10^{-7}M	10^{-6}M	1 mg/kg
14 (No. 51)	32.7	94,4		60.6

In Table 12, the compound in Example 14 is an R compound.

Table 13

Comp. of Ex. No. (Comp. No. in Table 5)	in vitro Inhibitory ratio (%)			ex vivo Inhibitory ratio (%)(p. o)
	1 0^{-7}M	3 x 10^{-7}M	10^{-6}M	1 mg/kg
16 (No. 53)	94.4	100		63.1

In Table 13, the compound in Example 16 is an R compound.

Experiment 3

Effects of 3,6-disubstituted pyridazine derivatives on on the myocardial infarction of a rat induced by the ligation of the left coronary artery

A rat group consisting of 8 male SD rats each weighing 200 to 250 g was tested. Myocardial infarction was produced in accordance with a method of Selye et al. That is, each rat was fixed on an operating boar on its back, and an about 1.5 cm incision had been made through the skin along the left sternal border under weak etherization. The pericardium was broken to exteriorize the heart, and the left coronary artery was ligated at a position of 1 to 2 mm apart from the origin thereof with black blade 4-O silk suture (produced by Hama Ika Kogyo). Thereafter, the heart was restored to

its original position and the chest was sutured. The air in the throacic cavity was discharged by pressing both side breast portions. After the resumption of respiration, the ST elevation in the standard limb lead II by an electrocardiograph (Model ECG-6601, produced by Nihon Koden Co.,). 24 hours after the ligation, blood was collected from the aortas at the abdomen. A fatal amount of blood was then drawn from each rat. The heart was taken out, and a tissue slice (about 2 mm thick) having an annular cross section was cut from the central portion of the heart. The tissue slice was incubated in 20 mℓ of 1% TTC (tryphenyl tetrazolium chloride, produced by Wako Pure Chemical Industries Limited) dissolved in 0.09 M of phosphoric acid buffer (pH 8.6) at 37°C for 20 minutes while shielding light. The tissue slice was photographed by a stereoscopic microscope to produce a color slide. The image of the tissue slice was projected on a wall surface from the color slide. The cut surface, the infarcted portion (portion not dyed with TTC) and the non-infarcted portion (portion dyed with TTC) were traced on a sheet, and the area of the infarcted portion in the whole cross section was calculated. The medicine was suspended in an aqueous 1% tragacanth solution and orally administered to each rat 60 minutes before the ligation of the left coronary artery.

The myocardial infarction inhibitory ratio was calculated from the following formula:

$$\text{Inhibitory ratio} = \frac{A - B}{A} \times 100\ (\%)$$

A: Infarction degree in the group (controlled group) to which only a solution of 1% tragacanth was administered
B: Infarction degree in the group to which the tragacanth solution containing a medicine was administered

The results are shown in Table 14.

Table 14

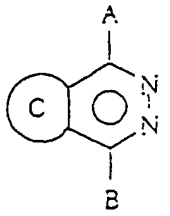
Compound No. (table 1)	doses (mg/kg)	percentage of inhibition
25 (R)	1	68.5
	3	82.2
Aspirin*	100	10.7
Ticlopidine*	30	10.1

*;anti-platelet aggregation agents

Claims

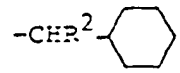
Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, PT, SE, IE

1. A 3,6-disubstituted pyridazine derivative represented by the following general formula (I), an optical antipode thereof and a pharmaceutically acceptable acid-additon salt thereof:



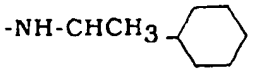
... (I)

wherein A represents a phenyl group, a thienyl group or a furyl group, each of which may be substituted by an alkyl group having 1 to 4 carbon atoms; B represents -NH-D [wherein D represents



(wherein R_2 represents an alkyl group having 1 to 4 carbon atoms); and the ring C represents a benzene ring; a furan ring: or a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms.

2. A compound according to claim 1, wherein A represents a phenyl group and B represents



3. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

4. A pharmaceutical composition for a disease caused by platelet agglutination, said composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

5. A pharmaceutical composition according to claim 4, wherein said disorder caused by platelet agglutination is ischemic heart disease.

6. A pharmaceutical composition according to claim 5, wherein said ischemic heart disease is myocardial infarction.

7. A pharmaceutical composition according to claim 5, wherein said ischemic heart disease is angina pectoris.

8. A pharmaceutical composition according to claim 4, wherein said disorder caused by platelet agglutination is cerebrovascular disorder.

9. A pharmaceutical composition according to claim 8, wherein said cerebrovascular disorder is cerebral thrombosis.

10. A pharmaceutical composition according to claim 8, wherein said cerebrovascular disorder is cerebral embolism.

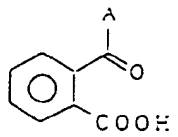
11. A pharmaceutical composition according to claim 4, wherein said disorder caused by platelet agglutination is a circulation disorder.

12. A pharmaceutical composition according to claim 11, wherein said circulation disorder is a peripheral circulation disorder.

13. A process for the manufacture of the compounds as defined in claim 1 or 2, **characterized by**

(i) when the ring C represents a benzene ring, reacting phthalic anhydride with

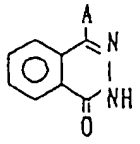
(a) a Grignard reagent or a lithium reagent of formula A-M
wherein A is as defined in claim 1 and M represents MgCl, MgBr, MgI or Li or
(b) with a compound of formula A-H
wherein A is as defined above to provide a compound of formula (X)



(X)

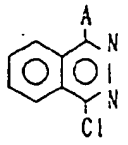
wherein A is as defined above,

reacting compound (X) with hydrazine or hydrazine hydrate to produce a compound of formula (XI)



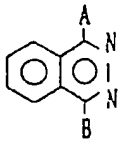
(XI)

wherein A is as defined above,
reacting compound (XI) with a chlorinating agent to provide a compound of formula (XII)



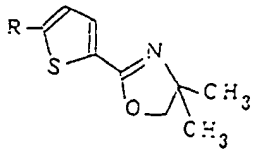
(XII)

wherein A is as defined above,
and reacting compound (XII) with a compound of the formula B-H, wherein B is as defined in claim 1 to produce a comDound of formula (I-a)



(I - a)

wherein A and B are as defined above,
or
(ii) when the ring C represents a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms, reacting a compound of formula (XIII)

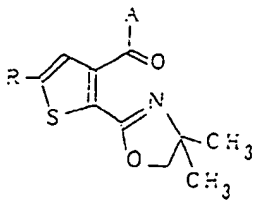


(XIII)

wherein R represents an alkyl group having 1 to 4 carbon atoms, with a base such as butyl lithium to produce an ortho-lithiated compound, which is then reacted with a compound represented by the general formula

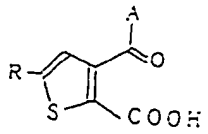
A-COR',

wherein A is as defined above and R' represents a halogen atom, an alkoxy group, an imidazolyl group or cyano group to produce a compound of for mula (XIV)



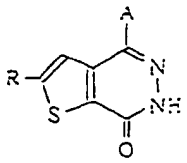
(XIV)

wherein A and R are as defined above,
cleaving the oxazoline ring of compound (XIV) to prepare a compound of formula (XV)



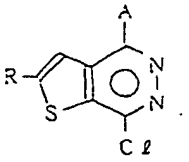
(XV)

wherein A and R are as defined above, and reacting the compound (XV) with hydrazine or hydrazine hydrate to produce a compound of formula (XVI)



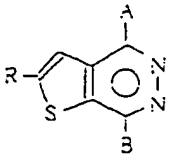
(XVI)

wherein R and A are as defined above,
reacting the compound (XVI) with a chlorinating agent to produce a compound of formula (XVII)



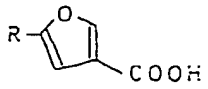
(XVII)

wherein A and R are as defined above and
reacting compound (XVII) with a compound of formula B-H,
wherein B is as defined above to produce a compound of formula (I-b)



(I - b)

wherein A, B and R are as defined above; or
(iii) when the ring C represents a furan ring which may be substituted by an alkyl group having 1 to 4 carbon atoms, reacting a compound of formula (XVIII)

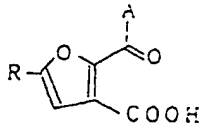


(XVIII)

wherein R represents an alkyl group having 1 to 4 carbon atoms, with a compound of formula (XIX)

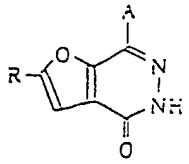
A-COR' (XIX),

wherein A is as defined above and R' represents a halogen atom, an alkoxy group, an aryloxy group. an imidazolyl group or a cyano group, to produce a compound of formula (XX)



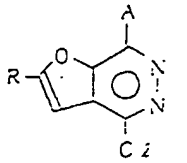
(XX)

wherein R and A are as defined above,
reacting compound (XX) with hydrazine or hydrazine hydrate to produce a compound of formula (XXI)



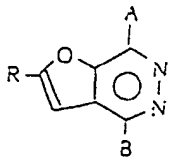
(XXI)

wherein R and A are as defined above,
reacting compound (XXI) with a chlorinating agent to produce a compound of formula (XXII)



(XXII)

wherein A and R are as defined above and
reacting compound (XXII) with a compound of formula B-H, wherein B is as defined above, to produce a compound of formula (I-c)

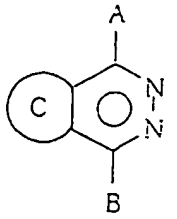


(I - c)

wherein A, B and R are as defined above.

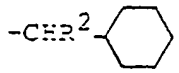
Claims for the following Contracting State : ES

1. A process for the manufacture of a 3,6-disubstituted pyridazine derivative represented by the following general formula (I), an optical antipode thereof and a pharmaceutically acceptable acid-addition salt thereof:



... (I)

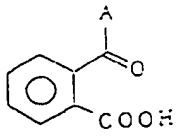
wherein A represents a phenyl group, a thienyl group or a furyl group, each of which may be substituted by an alkyl group having 1 to 4 carbon atoms; B represents -NH-D [wherein D represents



(wherein R_2 represents an alkyl group having 1 to 4 carbon atoms); and the ring C represents a benzene ring; a furan ring; or a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms, **characterized by**

(i) when the ring C represents a benzene ring, reacting phthalic anhydride with

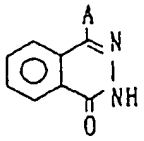
(a) a Grignard reagent or a lithium reagent of formula A-M
wherein A is as defined above and M represents MgCl MgBr, MgI or Li or
(b) with a compound of formula A-H
wherein A is as defined above to produce a compound of formula (X)



(X)

wherein A is as defined above,

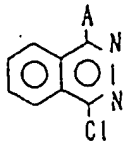
reacting compound (X) with hydrazine or hydrazine hydrate to produce a compound of formula (XI)



(XI)

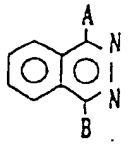
wherein A is as defined above.

reacting compound (XI) with a chlorinating agent to provide a compound of formula (XII)



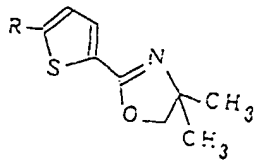
(XII)

wherein A is as defined above,
and reacting compound (XII) with a compound of the formula B-H, wherein B is as defined above to produce a compound of formula (I-a)



(I - a)

wherein A and B are as defined above,
or
(ii) when the ring C represents a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms, reacting a compound of formula (XIII)

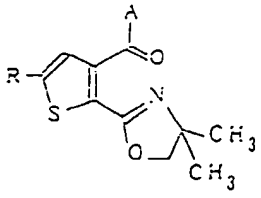


(XIII)

wherein R represents an alkyl group having 1 to 4 carbon atoms. with a base such as butyl lithium to produce an ortho-lithiated compound. which is then reacted with a compound represented by the general formula

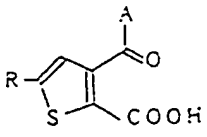
A-COR',

wherein A is as defined above and R' represents a halogen atom, an alkoxy group, an imidazolyl group or cyano group to produce a compound of for mula (XIV)



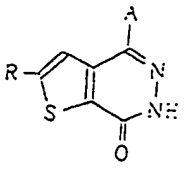
(XIV)

wherein A and R are as defined above,
cleaving the oxazoline ring of compound (XIV) to prepare a compound of formula (XV)



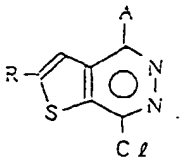
(XV)

wherein A and R are as defined above,
and reacting the compound (XV) with hydrazine or hydrazine hydrate to produce a compound of formula (XVI)



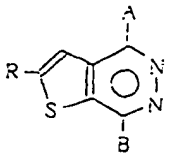
(XVI)

wherein R and A are as defined above,
reacting the compound (XVI) with a chlorinating agent to produce a compound of formula (XVII)



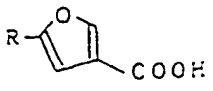
(XVII)

wherein A and R are as defined above and
reacting compound (XVII) with a compound of formula B-H,
wherein B is as defined above to produce a compound of formula (I-b)



(I - b)

wherein A, B and R are as defined above; or
(iii) when the ring C represents a furan ring which may be substituted by an alkyl group having 1 to 4 carbon atoms, reacting a compound of formula (XVIII)

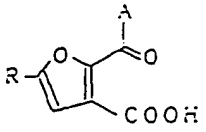


(XVIII)

wherein R represents an alkyl group having 1 to 4 carbon atoms, with a compound of formula (XIX)

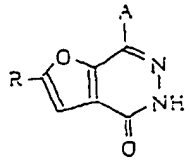
A-COR' (XIX),

wherein A is as defined above and R' represents a halogen atom, an alkoxy group, an aryloxy group, an imidazolyl group or a cyano group, to produce a compound of formula (XX)



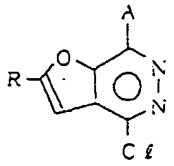
(XX)

wherein R and A are as defined above,
reacting compound (XX) with hydrazine or hydrazine hydrate to produce a compound of formula (XXI)



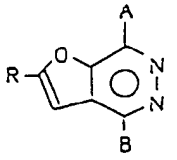
(XXI)

wherein R and A are as defined above,
reacting compound (XXI) with a chlorinating agent to produce a compound of formula (XXII)



(XXII)

wherein A and R are as defined above and
reacting compound (XXII) with a compound of formula B-H, wherein B is as defined above, to produce a compound of formula (I-c)

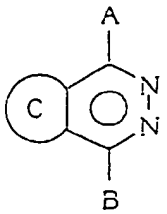


(I - c)

wherein A, B and R are as defined above.

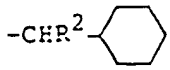
Claims for the following Contracting State : GR

1. A 3,6-disubstituted pyridazine derivative presented by the following general formula (I), an optical antipode thereof and pharmaceutically acceptable acid-addition salt thereof:



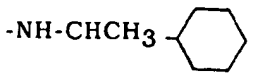
... (I)

wherein A represents a phenyl group, a thienyl group or a furyl group, each of which may be substituted by an alkyl group having 1 to 4 carbon atoms; B represents -NH-D [wherein D represents



(wherein R_2 represents an alkyl group having 1 to 4 carbon atoms); and the ring C represents a benzene ring; a furan ring; or a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms.

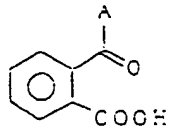
2. A compound according to claim 1, wherein A represents phenyl group and B represents



3. A process for the manufacture of the compounds as defined in claim 1 or 2, **characterized by**

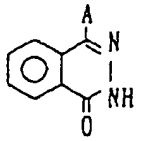
(i) when the ring C represents a benzene ring, reacting phthalic anhydride with

(a) a Grignard reagent or a lithium reagent of formula A-M
wherein A is as defined in claim 1 and M represents MgCl, MgBr. MgI or Li or
(b) with a compound of formula A-H
wherein A is as defined above to produce a compound of formula (X)



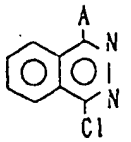
(X)

wherein A is as defined above,
reacting compound (X) with hydrazine or hydrazine hydrate to produce a compound of formula (XI)



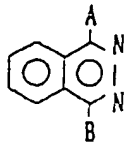
(XI)

wherein A is as defined above,
reacting compound (XI) with a chlorinating agent to provide a compound of formula (XII)



(XII)

wherein A is as defined above,
and reacting compound (XII) with a compound of the formula B-H, wherein B is as defined in claim 1 to produce a compound of formula (I-a)

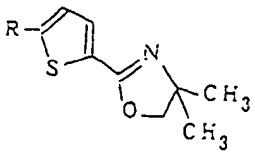


(I - a)

wherein A and B are as defined above,

or

(ii) when the ring C represents a thiophene ring which may be substituted by an alkyl group having 1 to 4 carbon atoms, reacting a compound of formula (XIII)

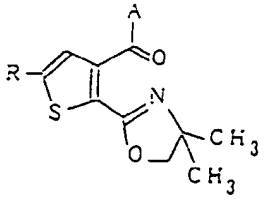


(XIII)

wherein R represents an alkyl group having 1 to 4 carbon atoms, with a base such as butyl lithium to produce an ortho-lithiated compound, which is then reacted with a compound represented by the general formula

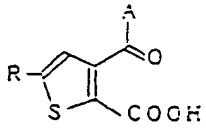
A-COR',

wherein A is as defined above and R' represents a halogen atom, an alkoxy group, an imidazolyl group or cyano group to produce a compound of formula (XIV)



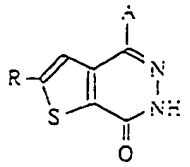
(XIV)

wherein A and R are as defined above,
cleaving the oxazoline ring of compound (XIV) to prepare a compound of formula (XV)



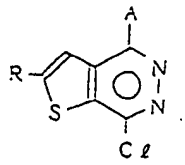
(XV)

wherein A and R are as defined above,
and reacting the compound (XV) with hydrazine or hydrazine hydrate to produce a compound of formula (XVI)



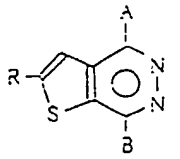
(XVI)

wherein R and A are as defined above, reacting the compound (XVI) with a chlorinating agent to produce a compound of formula (XVII)



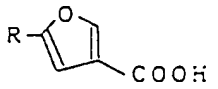
(XVII)

wherein A and R are as defined above and
reacting compound (XVII) with a compound of formula B-H,
wherein B is as defined above to produce a compound of formula (I-b)



(I - b)

wherein A, B and R are as defined above; or
(iii) when the ring C represents a furan ring which may be substituted by an alkyl group having 1 to 4 carbon atoms, reacting a compound of formula (XVIII)

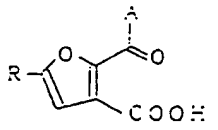


(XVIII)

wherein R represents an alkyl group having 1 to 4 carbon atoms, with a compound of formula (XIX)

A-COR' (XIX),

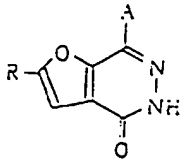
wherein A is as defined above and R' represents a halogen atom, an alkoxy group, an aryloxy group, an imidazolyl group or a cyano group, to produce a compound of formula (XX)



(XX)

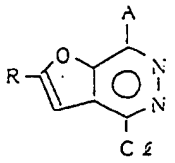
wherein R and A are as defined above,

reacting compound (XX) with hydrazine or hydrazine hydrate to produce a compound of formula (XXI)



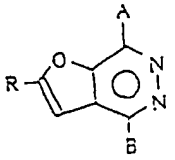
(XXI)

wherein R and A are as defined above,
reacting compound (XXI) with a chlorinating agent to produce a compound of formula (XXII)



(XXII)

wherein A and R are as defined above and
reacting compound (XXII) with a compound of formula B-H,
wherein B is as defined above, to produce a compound of formula (I-c)



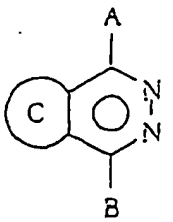
(I - c)

wherein A, B and R are as defined above.

Patentansprüche

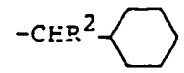
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, PT, SE, IE

1. 3,6-Disubstituiertes Pyridazinderivat der folgenden allgemeinen Formel (I), optischer Antipode hiervon und ein pharmazeutisch annehmbares Säureadditionssalz hiervon:



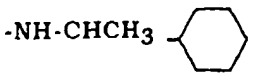
... (I)

worin A eine Phenylgruppe, eine Thienylgruppe oder eine Furylgruppe bedeutet, die jeweils durch eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein können; B die Bedeutung -NH-D hat (worin D



(worin R^2 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen bedeutet) bedeutet]; und der Ring C einen Benzolring; einen Furanring; oder einen Thiophenring bedeutet, welcher durch eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein kann.

2. Verbindung nach Anspruch 1, wobei A eine Phenylgruppe bedeutet und B



bedeutet.

3. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach Anspruch 1 und einen pharmazeutisch annehmbaren Träger.

4. Pharmazeutische Zusammensetzung für eine durch Blutplättchenagglutination verursachte Krankheit, wobei die Zusammensetzung eine Verbindung nach Anspruch 1 und einen pharmazeutisch annehmbaren Träger umfaßt.

5. Pharmazeutische Zusammensetzung nach Anspruch 4, wobei die durch Blutplättchenagglutination verursachte Störung eine ischämische Herzkrankheit ist.

6. Pharmazeutische Zusammensetzung nach Anspruch 5, wobei die ischämische Herzkrankheit Myokardinfarkt ist.

7. Pharmazeutische Zusammensetzung nach Anspruch 5, wobei die ischämische Herzkrankheit Angina Pectoris ist.

8. Pharmazeutische Zusammensetzung nach Anspruch 4, wobei die durch Blutplättchenagglutination verursachte Störung eine zerebrovaskuläre Störung ist.

9. Pharmazeutische Zusammensetzung nach Anspruch 8, wobei die zerebrovaskuläre Störung Zerebralthrombose ist.

10. Pharmazeutische Zusammensetzung nach Anspruch 8, wobei die zerebrovaskuläre Störung Zerebralembolie ist.

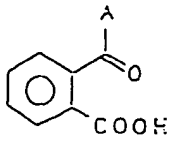
11. Pharmazeutische Zusammensetzung nach Anspruch 4, wobei die durch Blutplättchenagglutination verursachte Störung eine Kreislaufstörung ist.

12. Pharmazeutische Zusammensetzung nach Anspruch 11, wobei die Kreislaufstörung eine periphere Kreislaufstörung ist.

13. Verfahren zur Herstellung der Verbindungen nach Anspruch 1 oder 2, gekennzeichnet durch

(i) wenn der Ring C einen Benzolring bedeutet, Umsetzen von Phthalsäureanhydrid mit

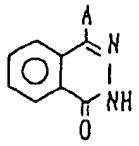
(a) einem Grignard-Reagens oder einem Lithium-Reagens der Formel A-M,
worin A wie in Anspruch 1 definiert ist, und M MgCl, MgBr, MgI oder Li bedeutet, oder
(b) mit einer Verbindung der Formel A-H,
worin A wie oben definiert ist, um eine Verbindung der Formel (X) vorzusehen



(X)

worin A wie oben definiert ist,

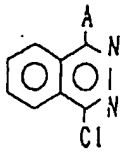
Umsetzen der Verbindung (X) mit Hydrazin oder Hydrazinhydrat, um eine Verbindung der Formel (XI) zu erzeugen



(XI)

worin A wie oben definiert ist,

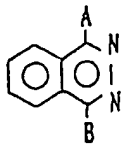
Umsetzen der Verbindung (XI) mit einem Chlorierungsmittel, um eine Verbindung der Formel (XII) vorzusehen



(XII)

worin A wie oben definiert ist,

und Umsetzen der Verbindung (XII) mit einer Verbindung der Formel B-H, worin B wie in Anspruch 1 definiert ist, um eine Verbindung der Formel (I-a) zu erzeugen

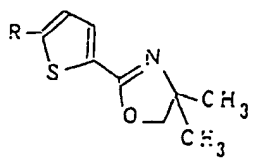


(I - a)

worin A und B wie oben definiert sind,

oder

(ii) wenn der Ring C einen Thiophenring bedeutet, welcher durch eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein kann, Umsetzen einer Verbindung der Formel (XIII)

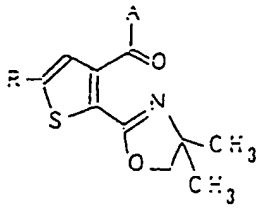


(XIII)

worin R eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen bedeutet, mit einer Base, wie Butyllithium, um eine ortho-Lithiumverbindung zu erzeugen, welche dann mit einer Verbindung der allgemeinen Formel

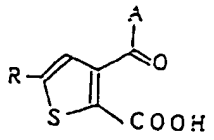
A-COR',

worin A wie oben definiert ist und R' ein Halogenatom, eine Alkoxygruppe, eine Imidazolylgruppe oder Cyanogruppe bedeutet, umgesetzt wird, um eine Verbindung der Formel (XIV) zu erzeugen



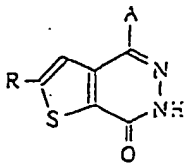
(XIV)

worin A und R wie oben definiert sind,
Spalten des Oxazolinrings der Formel (XIV), um eine Verbindung der Formel (XV) herzustellen



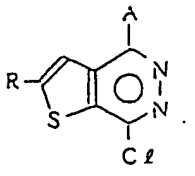
(XV)

worin A und R wie oben definiert sind,
und Umsetzen der Verbindung (XV) mit Hydrazin oder Hydrazinhydrat, um eine Verbindung der Formel (XVI) zu erzeugen



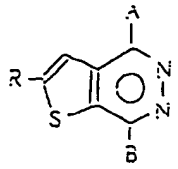
(XVI)

worin R und A wie oben definiert sind,
Umsetzen der Verbindung (XVI) mit einem Chlorierungsmittel, um eine Verbindung der Formel (XVII) herzustellen



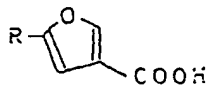
(XVII)

worin A und R wie oben definiert sind und
Umsetzen der Verbindung (XVII) mit einer Verbindung der Formel B-H,
worin B wie oben definiert ist, um eine Verbindung der Formel (I-b) herzustellen



(I - b)

worin A, B und R wie oben definiert sind; oder
(iii) wenn der Ring C einen Furanring bedeutet, welcher durch eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein kann, Umsetzen einer Verbindung der Formel (XVIII)

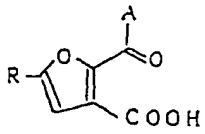


(XVIII)

worin R eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen bedeutet, mit einer Verbindung der Formel (XIX)

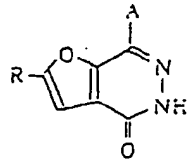
A-COR' (XIX)

worin A wie oben definiert ist, und R' ein Halogenatom, eine Alkoxygruppe, eine Aryloxygruppe, eine Imidazolylgruppe oder eine Cyanogruppe bedeutet, um eine Verbindung der Formel (XX) herzustellen



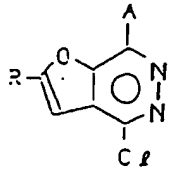
(XX)

worin R und A wie oben definiert sind,
Umsetzen der Verbindung (XX) mit Hydrazin oder Hydrazinhydrat, um eine Verbindung der Formel (XXI) herzustellen



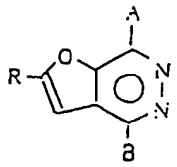
(XXI)

worin R und A wie oben definiert sind,
Umsetzen der Verbindung (XXI) mit einem Chlorierungsmittel, um eine Verbindung der Formel (XXII) herzustellen



(XXII)

worin A und R wie oben definiert sind, und
Umsetzen der Verbindung (XXII) mit einer Verbindung der Formel B-H, worin B wie oben definiert ist, um eine Verbindung der Formel (I-c) herzustellen

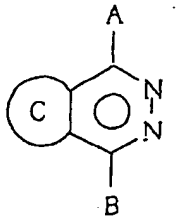


(I - c)

worin A, B und R wie oben definiert sind.

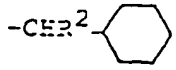
Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung eines 3,6-disubstituierten Pyridazinderivats der folgenden allgemeinen Formel (I), eines optischen Antipoden hiervon und eines pharmazeutisch annehmbaren Säureadditionssalzes hiervon:



... (I)

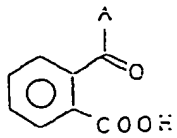
worin A eine Phenylgruppe, eine Thienylgruppe oder eine Furylgruppe bedeutet, die jeweils durch eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein können; B die Bedeutung -NH-D hat [worin D



(worin R_2 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen bedeutet) bedeutet]; und der Ring C einen Benzolring; einen Furanring; oder einen Thiophenring bedeutet, welcher durch eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein kann,
gekennzeichnet durch

(i) wenn der Ring C einen Benzolring bedeutet, Umsetzen von Phthalsäureanhydrid mit

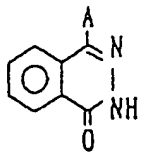
(a) einem Grignard-Reagens oder einem Lithium-Reagens der Formel A-M,
worin A wie oben definiert ist, und M MgCl, MgBr, MgI oder Li bedeutet, oder
(b) mit einer Verbindung der Formel A-H,
worin A wie oben definiert ist, um eine Verbindung der Formel (X) vorzusehen



(X)

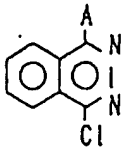
worin A wie oben definiert ist,

Umsetzen der Verbindung (X) mit Hydrazin oder Hydrazinhydrat, um eine Verbindung der Formel (XI) zu erzeugen



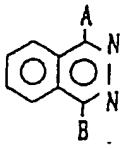
(XI)

worin A wie oben definiert ist,
Umsetzen der Verbindung (XI) mit einem Chlorierungsmittel, um eine Verbindung der Formel (XII) vorzusehen



(XII)

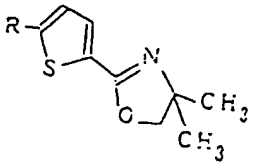
worin A wie oben definiert ist,
und Umsetzen der Verbindung (XII) mit einer Verbindung der Formel B-H, worin B wie oben definiert ist, um eine Verbindung der Formel (I-a) zu erzeugen



(I - a)

worin A und B wie oben definiert sind,
oder

(ii) wenn der Ring C einen Thiophenring bedeutet, welcher durch eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein kann, Umsetzen einer Verbindung der Formel (XIII)

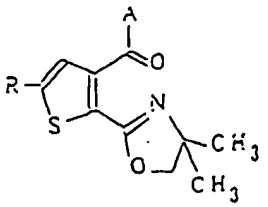


(XIII)

worin R eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen bedeutet, mit einer Base, wie Butyllithium, um eine ortho-Lithiumverbindung zu erzeugen, welche dann mit einer Verbindung der allgemeinen Formel

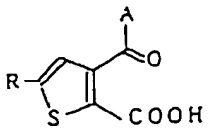
A-COR',

worin A wie oben definiert ist und R' ein Halogenatom, eine Alkoxygruppe, eine Imidazolylgruppe oder Cyanogruppe bedeutet, umgesetzt wird, um eine Verbindung der Formel (XIV) zu erzeugen



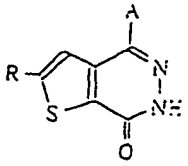
(XIV)

worin A und R wie oben definiert sind,
Spalten des Oxazolinrings der Formel (XIV), um eine Verbindung der Formel (XV) herzustellen



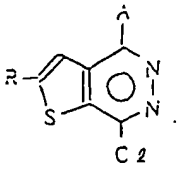
(XV)

worin A und R wie oben definiert sind,
und Umsetzen der Verbindung (XV) mit Hydrazin oder Hydrazinhydrat, um eine Verbindung der Formel (XVI) zu erzeugen



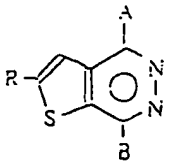
(XVI)

worin R und A wie oben definiert sind,
Umsetzen der Verbindung (XVI) mit einem Chlorierungsmittel, um eine Verbindung der Formel (XVII) herzustellen



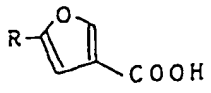
(XVII)

worin A und R wie oben definiert sind und
Umsetzen der Verbindung (XVII) mit einer Verbindung der Formel B-H,
worin B wie oben definiert ist, um eine Verbindung der Formel (I-b) herzustellen



(I - b)

worin A, B und R wie oben definiert sind; oder
(iii) wenn der Ring C einen Furanring bedeutet, welcher durch eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein kann, Umsetzen einer Verbindung der Formel (XVIII)

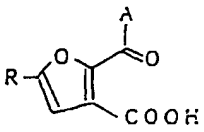


(XVIII)

worin R eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen bedeutet, mit einer Verbindung der Formel (XIX)

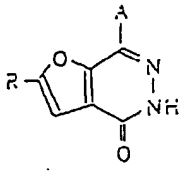
A-COR' (XIX)

worin A wie oben definiert ist, und R' ein Halogenatom, eine Alkoxygruppe, eine Aryloxygruppe, eine Imidazolylgruppe oder eine Cyanogruppe bedeutet, um eine Verbindung der Formel (XX) herzustellen



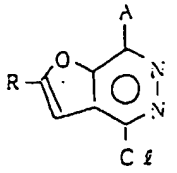
(XX)

worin R und A wie oben definiert sind,
Umsetzen der Verbindung (XX) mit Hydrazin oder Hydrazinhydrat, um eine Verbindung der Formel (XXI) herzustellen



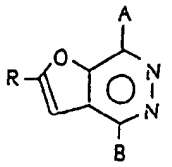
(XXI)

worin R und A wie oben definiert sind,
Umsetzen der Verbindung (XXI) mit einem Chlorierungsmittel, um eine Verbindung der Formel (XXII) herzustellen



(XXII)

worin A und R wie oben definiert sind, und
Umsetzen der Verbindung (XXII) mit einer Verbindung der Formel B-H, worin B wie oben definiert ist, um eine Verbindung der Formel (I-c) herzustellen

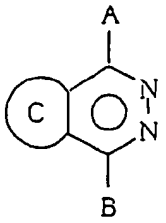


(I - c)

worin A, B und R wie oben definiert sind.

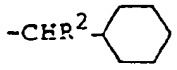
Patentansprüche für folgenden Vertragsstaat : GR

1. 3,6-Disubstituiertes Pyridazinderivat der folgenden allgemeinen Formel (I), optischer Antipode hiervon und ein pharmazeutisch annehmbares Säureadditionssalz hiervon:



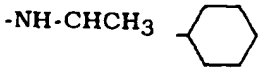
... (I)

worin A eine Phenylgruppe, eine Thienylgruppe oder eine Furylgruppe bedeutet, die jeweils durch eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein können; B die Bedeutung -NH-D hat [worin D



(worin R_2 eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen bedeutet) bedeutet]; und der Ring C einen Benzolring; einen Furanring; oder einen Thiophenring bedeutet, welcher durch eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein kann.

2. Verbindung nach Anspruch 1, wobei A eine Phenylgruppe bedeutet und B

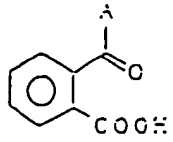


bedeutet.

3. Verfahren zur Herstellung der Verbindungen nach Anspruch 1 oder 2, gekennzeichnet durch

(i) wenn der Ring C einen Benzolring bedeutet, Umsetzen von Phthalsäureanhydrid mit

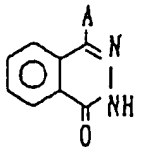
(a) einem Grignard-Reagens oder einem Lithium-Reagens der Formel A-M,
worin A wie in Anspruch 1 definiert ist, und M MgCl, MgBr, MgI oder Li bedeutet, oder
(b) mit einer Verbindung der Formel A-H,
worin A wie oben definiert ist, um eine Verbindung der Formel (X) vorzusehen



(X)

worin A wie oben definiert ist,

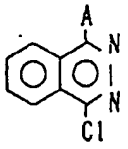
Umsetzen der Verbindung (X) mit Hydrazin oder Hydrazinhydrat, um eine Verbindung der Formel (XI) zu erzeugen



(XI)

worin A wie oben definiert ist,

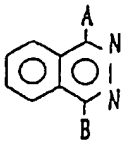
Umsetzen der Verbindung (XI) mit einem Chlorierungsmittel, um eine Verbindung der Formel (XII) vorzusehen



(XII)

worin A wie oben definiert ist,

und Umsetzen der Verbindung (XII) mit einer Verbindung der Formel B -H, worin B wie in Anspruch 1 definiert ist, um eine Verbindung der Formel (I-a) zu erzeugen

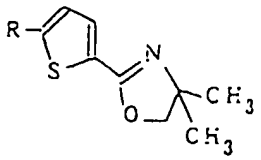


(I - a)

worin A und B wie oben definiert sind,

oder

(ii) wenn der Ring C einen Thiophenringbedeutet, welcher durch eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein kann, Umsetzen einer Verbindung der Formel (XIII)

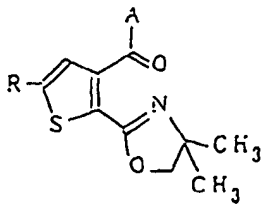


(XIII)

worin R eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen bedeutet, mit einer Base, wie Butyllithium, um eine ortho-Lithiumverbindung zu erzeugen, welche dann mit einer Verbindung der allgemeinen Formel

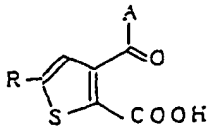
A-COR',

worin A wie oben definiert ist und R' ein Halogenatom, eine Alkoxygruppe, eine Imidazolylgruppe oder Cyanogruppe bedeutet, umgesetzt wird, um eine Verbindung der Formel (XIV) zu erzeugen



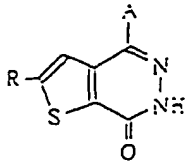
(XIV)

worin A und R wie oben definiert sind,
Spalten des Oxazolinrings der Formel (XIV), um eine Verbindung der Formel (XV) herzustellen



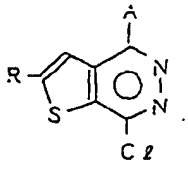
(XV)

worin A und R wie oben definiert sind,
und Umsetzen der Verbindung (XV) mit Hydrazin oder Hydrazinhydrat, um eine Verbindung der Formel (XVI) zu erzeugen



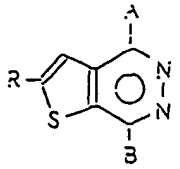
(XVI)

worin R und A wie oben definiert sind,
Umsetzen der Verbindung (XVI) mit einem Chlorierungsmittel, um eine Verbindung der Formel (XVII) herzustellen



(XVII)

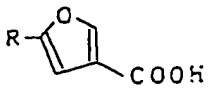
worin A und R wie oben definiert sind und
Umsetzen der Verbindung (XVII) mit einer Verbindung der Formel B-H,
worin B wie oben definiert ist, um eine Verbindung der Formel (I-b) herzustellen



(I - b)

worin A, B und R wie oben definiert sind; oder

(iii) wenn der Ring C einen Furanring bedeutet, welcher durch eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen substituiert sein kann, Umsetzen einer Verbindung der Formel (XVIII)

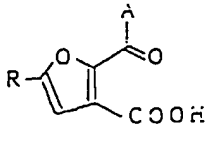


(XVIII)

worin R eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen bedeutet, mit einer Verbindung der Formel (XIX)

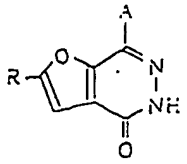
A-COR' (XIX)

worin A wie oben definiert ist, und R' ein Halogenatom, eine Alkoxygruppe, eine Aryloxygruppe, eine Imidazolylgruppe oder eine Cyanogruppe bedeutet, um eine Verbindung der Formel (XX) herzustellen



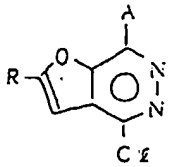
(XX)

worin R und A wie oben definiert sind,
Umsetzen der Verbindung (XX) mit Hydrazin oder Hydrazinhydrat, um eine Verbindung der Formel (XXI) herzustellen



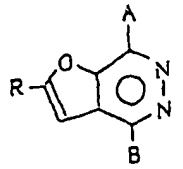
(XXI)

worin R und A wie oben definiert sind,
Umsetzen der Verbindung (XXI) mit einem Chlorierungsmittel, um eine Verbindung der Formel (XXII) herzustellen



(XXII)

worin A und R wie oben definiert sind, und
Umsetzen der Verbindung (XXII) mit einer Verbindung der Formel B-H, worin B wie oben definiert ist, um eine Verbindung der Formel (I-c) herzustellen



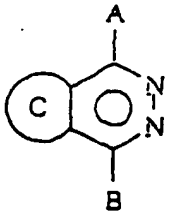
(I - c)

worin A, B und R wie oben definiert sind.

Revendications

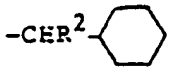
Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, PT, SE, IE

1. Dérivé de pyridazine 3,6-disubstituée représenté par la formule générale (I) suivante, antipode optique de celui-ci, et sel d'addition de celui-ci avec un acide pharmaceutiquement acceptable :



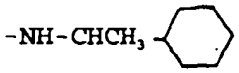
... (I)

dans laquelle A représente un groupe phényle, un groupe thiényle ou un groupe furyle, chacun de ceux-ci pouvant être substitué par un groupe alkyle comportant de 1 à 4 atomes de carbone ; B représente -NH-D (D représentant :



R_2 représentant un groupe alkyle comportant de 1 à 4 atomes de carbone) ; et le noyau C représentant un cycle benzénique ; un cycle furanne ; ou un cycle thiophène qui peut être substitué par un groupe alkyle comportant de 1 à 4 atomes de carbone.

2. Composé selon la revendication 1, dans lequel A représente un groupe phényle et B représente



3. Composition pharmaceutique comprenant un composé selon la revendication 1 et un véhicule pharmaceutiquement acceptable.

4. Composition pharmaceutique pour les maladies dues à l'agglutination de plaquettes, ladite composition comprenant un composé selon la revendication 1 et un véhicule pharmaceutiquement acceptable.

5. Composition pharmaceutique selon la revendication 4, dans laquelle lesdites affections dues à l'agglutination de

plaquettes, comprennent les cardiopathies ischémiques.

6. Composition pharmaceutique selon la revendication 5, dans laquelle lesdites cardiopathies ischémiques comprennent l'infarctus du myocarde.

7. Composition pharmaceutique selon la revendication 5, dans laquelle lesdites cardiopathies ischémiques comprennent l'angine de poitrine.

8. Composition pharmaceutique selon la revendication 4, dans laquelle lesdites affections dues à l'agglutination de plaquettes, comprennent les troubles cérébrovasculaires.

9. Composition pharmaceutique selon la revendication 8, dans laquelle lesdits troubles cérébrovasculaires comprennent la thrombose cérébrale.

10. Composition pharmaceutique selon la revendication 8, dans laquelle lesdits troubles cérébrovasculaires comprennent l'embolie cérébrale.

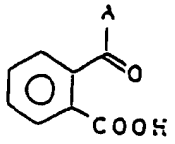
11. Composition pharmaceutique selon la revendication 4, dans laquelle lesdites affections dues à l'agglutination de plaquettes comprennent les troubles de la circulation.

12. Composition pharmaceutique selon la revendication 11, dans laquelle lesdits troubles de la circulation comprennent les troubles de la circulation périphérique.

13. Procédé de fabrication des composés selon la revendication 1 ou 2, caractérisé en ce que :

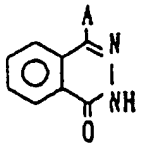
(i) lorsque le noyau C représente un cycle benzénique, on fait réagir de l'anhydride phtalique avec :

(a) un réactif de Grignard ou un réactif lithié de formule A-M dans laquelle A est tel que défini dans la revendication 1, et M représente MgCl, MgBr, MgI ou Li, ou
(b) avec un composé de formule A-H dans laquelle A est tel que défini ci-dessus, pour former un composé de formule (X) :



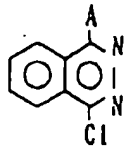
(X)

dans laquelle A est tel que défini ci-dessus, on fait réagir le composé (X) avec de l'hydrazine ou de l'hydrate d'hydrazine pour produire un composé de formule (XI) :



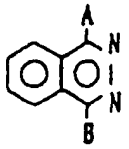
(XI)

dans laquelle A est tel que défini ci-dessus, on fait réagir le composé (XI) avec un agent chlorant pour obtenir un composé de formule (XII) :



(XII)

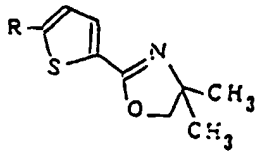
dans laquelle A est tel que défini ci-dessus, et on fait réagir le composé (XII) avec un composé de formule B-H, dans laquelle B est tel que défini dans la revendication 1, pour produire un composé de formule (I-a) :



(I - a)

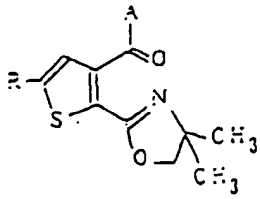
dans laquelle A et B sont tels que définis ci-dessus, ou

(ii) lorsque le noyau C représente un cycle thiophène qui peut être substitué par un groupe alkyle comportant de 1 à 4 atomes de carbone, on fait réagir un composé de formule (XIII) :



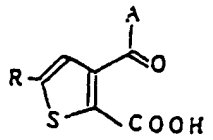
(XIII)

dans laquelle R représente un groupe alkyle comportant de 1 à 4 atomes de carbone, avec une base telle que le butyllithium, pour produire un composé ortho-lithié, que l'on fait ensuite réagir avec un composé représenté par la formule générale A-COR', dans laquelle A est tel que défini ci-dessus, et R' représente un atome d'halogène, un groupe alkoxy, un groupe imidazolyle ou un groupe cyano, pour produire un composé de formule (XIV) :



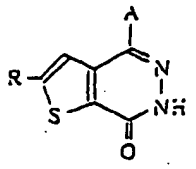
(XIV)

dans laquelle A et R sont tels que définis ci-dessus,
on coupe le cycle oxazoline du composé (XIV) pour préparer un composé de formule (XV) :



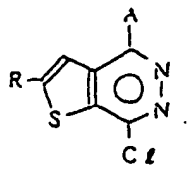
(XV)

dans laquelle A et R sont tels que définis ci-dessus, et
on fait réagir le composé (XV) avec de l'hydrazine ou de l'hydrate d'hydrazine, pour produire un composé de formule (XVI) :



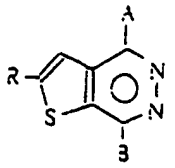
(XVI)

dans laquelle R et A sont tels que définis ci-dessus,
on fait réagir le composé (XVI) avec un agent chlorant pour produire un composé de formule (XVII) :



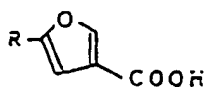
(XVII)

dans laquelle A et R sont tels que définis ci-dessus, et
on fait réagir le composé (XVII) avec un composé de formule B-H,
dans laquelle B est tel que défini ci-dessus, pour produire un composé de formule (I-b) :



(I - b)

dans laquelle A, B et R sont tels que définis ci-dessus ; ou
(iii) lorsque le noyau C représente un cycle furanne qui peut être substitué par un groupe alkyle comportant de 1 à 4 atomes de carbone, on fait réagir un composé de formule (XVIII) :

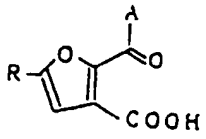


(XVIII)

dans laquelle R représente un groupe alkyle comportant de 1 à 4 atomes de carbone, avec un composé de formule (XIX) :

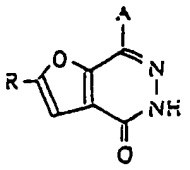
A-COR' (XIX),

dans laquelle A est tel que défini ci-dessus, et R' représente un atome d'halogène, un groupe alkoxy, un groupe aryloxy, un groupe imidazolyle ou un groupe cyano, pour produire un composé de formule (XX) :



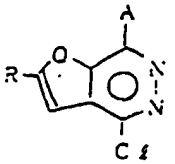
(XX)

dans laquelle R et A sont tels que définis ci-dessus,
on fait réagir le composé (XX) avec de l'hydrazine ou de l'hydrate d'hydrazine, pour produire un composé de formule (XXI) :



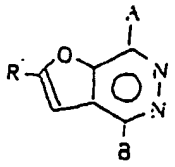
(XXI)

dans laquelle R et A sont tels que définis ci-dessus,
on fait réagir un composé (XXI) avec un agent chlorant pour produire un composé de formule (XXII) :



(XXII)

dans laquelle A et R sont tels que définis ci-dessus, et
on fait réagir le composé (XXII) avec un composé de formule B-H, dans laquelle B est tel que défini ci-dessus, pour produire un composé de formule (I-c) :

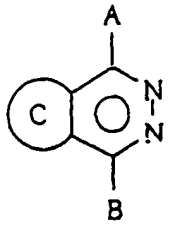


(I - c)

dans laquelle A, B et R sont tels que définis ci-dessus.

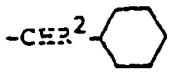
Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'un dérivé de pyridazine 3,6-disubstituée représenté par la formule générale (I) suivante, d'un antipode optique de celui-ci et d'un sel d'addition de celui-ci avec un acide pharmaceutiquement acceptable :



... (I)

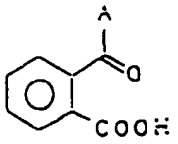
dans laquelle A représente un groupe phényle, un groupe thiényle ou un groupe furyle, chacun de ceux-ci pouvant être substitué par un groupe alkyle comportant de 1 à 4 atomes de carbone ; B représente -NH-D (D représentant :



(dans laquelle R_2 représente un groupe alkyle comportant de 1 à 4 atomes de carbone) ; et le noyau C représente un cycle benzénique ; un cycle furanne ; ou un cycle thiophène, qui peut être substitué par un groupe alkyle comportant de 1 à 4 atomes de carbone, caractérisé en ce que :

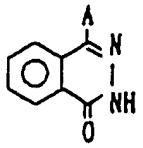
(i) lorsque le noyau C représente un cycle benzénique, on fait réagir de l'anhydride phtalique avec :

(a) un réactif de Grignard ou un réactif lithié de formule A-M dans laquelle A est tel que défini ci-dessus, et M représente MgCl, MgBr, MgI ou Li, ou
(b) avec un composé de formule A-H dans laquelle A est tel que défini ci-dessus, pour produire un composé de formule (X) :



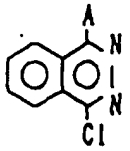
(X)

dans laquelle A est tel que défini ci-dessus, on fait réagir le composé (X) avec de l'hydrazine ou de l'hydrate d'hydrazine, pour produire un composé de formule (XI) :



(XI)

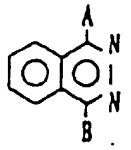
dans laquelle A est tel que défini ci-dessus, on fait réagir le composé (XI) avec un agent chlorant, pour obtenir un composé de formule (XII) :



(XII)

dans laquelle A est tel que défini ci-dessus, et on fait réagir le composé (XII) avec un composé de

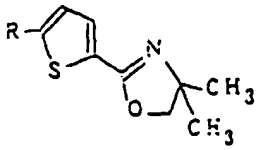
formule B-H, dans laquelle B est tel que défini ci-dessus, pour produire un composé de formule (I-a) :



(I - a)

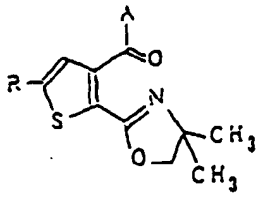
dans laquelle A et B sont tels que définis ci-dessus, ou

(ii) lorsque le noyau C représente un cycle thiophène qui peut être substitué par un groupe alkyle comportant de 1 à 4 atomes de carbone, on fait réagir un composé de formule (XIII) :



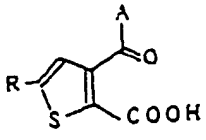
(XIII)

dans laquelle R représente un groupe alkyle comportant de 1 à 4 atomes de carbone, avec une base telle que le butyllithium, pour produire un composé ortho-lithié que l'on fait ensuite réagir avec un composé représenté par la formule générale A-COR', dans laquelle A est tel que défini ci-dessus, et R' représente un atome d'halogène, un groupe alkoxy, un groupe imidazolyle ou un groupe cyano, pour produire un composé de formule (XIV) :



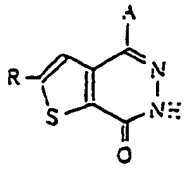
(XIV)

dans laquelle A et R sont tels que définis ci-dessus,
on coupe le cycle oxazoline du composé (XIV) pour préparer un composé de formule (XV) :



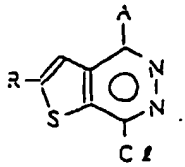
(XV)

dans laquelle A et R sont tels que définis ci-dessus, et
on fait réagir le composé (XV) avec de l'hydrazine ou de l'hydrate d'hydrazine, pour produire un composé de formule (XVI) :



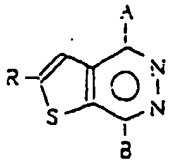
(XVI)

dans laquelle R et A sont tels que définis ci-dessus,
on fait réagir le composé (XVI) avec un agent chlorant pour produire un composé de formule (XVII) :



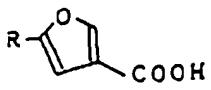
(XVII)

dans laquelle A et R sont tels que définis ci-dessus, et
on fait réagir le composé (XVII) avec un composé de formule B-H,
dans laquelle B est tel que défini ci-dessus, pour produire un composé de formule (I-b) :



(I - b)

dans laquelle A, B et R sont tels que définis ci-dessus ; ou
(iii) lorsque le noyau C représente un cycle furanne qui peut être substitué par un groupe alkyle comportant de 1 à 4 atomes de carbone, on fait réagir un composé de formule (XVIII) :

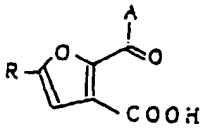


(XVIII)

dans laquelle R représente un groupe alkyle comportant de 1 à 4 atomes de carbone, avec un composé de formule (XIX) :

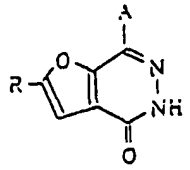
A-COR' (XIX),

dans laquelle A est tel que défini ci-dessus, et R' représente un atome d'halogène, un groupe alkoxy, un groupe aryloxy, un groupe imidazolyle ou un groupe. cyano, pour produire un composé de formule (XX) :



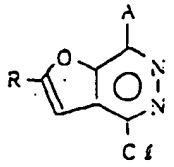
(XX)

dans laquelle R et A sont tels que définis ci-dessus,
on fait réagir le composé (XX) avec de l'hydrazine ou de l'hydrate d'hydrazine, pour produire un composé de formule (XXI) :



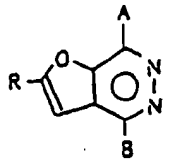
(XXI)

dans laquelle R et A sont tels que définis ci-dessus,
on fait réagir le composé (XXI) avec un agent chlorant pour produire un composé de formule (XXII) :



(XXII)

dans laquelle A et R sont tels que définis ci-dessus, et
on fait réagir le composé (XXII) avec un composé de formule B-H, dans laquelle B est tel que défini ci-dessus, pour produire un composé de formule (I-c) :

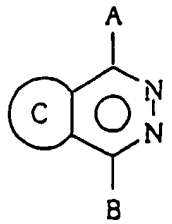


(I - c)

dans laquelle A, B et R sont tels que définis ci-dessus.

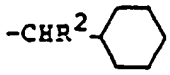
Revendications pour l'Etat contractant suivant : GR

1. Dérivé de pyridazine 3,6-disubstituée, représenté par la formule générale (I) suivante, antipode optique de celui-ci et sel d'addition de celui-ci avec un acide pharmaceutiquement acceptable :



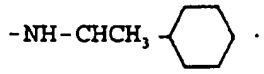
... (I)

dans laquelle A représente un groupe phényle, un groupe thiényle ou un groupe furyle, chacun de ceux-ci pouvant être substitué par un groupe alkyle comportant de 1 à 4 atomes de carbone ; B représente -NH-D (D représentant :



(dans laquelle R_2 représente un groupe alkyle comportant de 1 à 4 atomes de carbone) ; et le noyau C représente un cycle benzénique ; un cycle furanne ; ou un cycle thiophène, qui peut être substitué par un groupe alkyle comportant de 1 à 4 atomes de carbone.

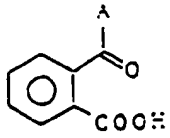
2. Composé selon la revendication 1, dans lequel A représente un groupe phényle et B représente



3. Procédé de fabrication des composés selon la revendication 1 ou 2, caractérisé en ce que :

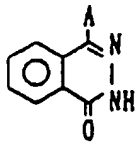
(i) lorsque le noyau C représente un cycle benzénique, on fait réagir de l'anhydride phtalique avec :

(a) un réactif de Grignard ou un réactif lithié de formule A-M dans laquelle A est tel que défini dans la revendication 1, et M représente MgCl, MgBr, MgI ou Li, ou
(b) avec un composé de formule A-H dans laquelle A est tel que défini ci-dessus, pour produire un composé de formule (X) :



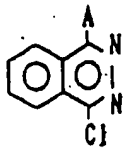
(X)

dans laquelle A est tel que défini ci-dessus, on fait réagir le composé (X) avec de l'hydrazine ou de l'hydrate d'hydrazine, pour produire un composé de formule (XI) :



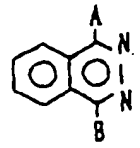
(XI)

dans laquelle A est tel que défini ci-dessus, on fait réagir le composé (XI) avec un agent chlorant, pour produire un composé de formule (XII) :



(XII)

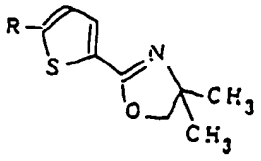
dans laquelle A est tel que défini ci-dessus, et on fait réagir le composé (XII) avec un composé de formule B-H, dans laquelle B est tel que défini dans la revendication 1, pour produire un composé de formule (I-a) :



(I - a)

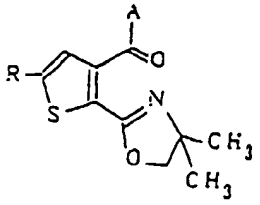
dans laquelle A et B sont tels que définis ci-dessus, ou

(ii) lorsque le noyau C représente un cycle thiophène qui peut être substitué par un groupe alkyle comportant de 1 à 4 atomes de carbone, on fait réagir un composé de formule (XIII) :



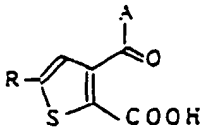
(XIII)

dans laquelle R représente un groupe alkyle comportant de 1 à 4 atomes de carbone, avec une base telle que le butyllithium, pour produire un composé ortho-lithié que l'on fait ensuite réagir avec un composé représenté par la formule générale A-COR', dans laquelle A est tel que défini ci-dessus, et R' représente un atome d'halogène, un groupe alkoxy, un groupe imidazolyle ou un groupe cyano, pour produire un composé de formule (XIV) :



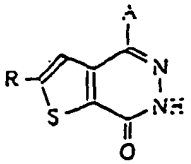
(XIV)

dans laquelle A et R sont tels que définis ci-dessus,
on coupe le cycle oxazoline du composé (XIV) pour préparer un composé de formule (XV) :



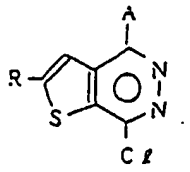
(XV)

dans laquelle A et R sont tels que définis ci-dessus, et
on fait réagir le composé (XV) avec de l'hydrazine ou de l'hydrate d'hydrazine, pour produire un composé de formule (XVI) :



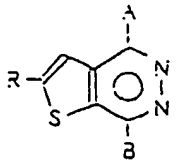
(XVI)

dans laquelle R et A sont tels que définis ci-dessus,
on fait réagir le composé (XVI) avec un agent chlorant pour produire un composé de formule (XVII) :



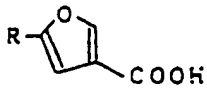
(XVII)

dans laquelle A et R sont tels que définis ci-dessus, et
on fait réagir le composé (XVII) avec un composé de formule B-H,
dans laquelle B est tel que défini ci-dessus, pour préparer un composé de formule (I-b) :



(I - b)

dans laquelle A, B et R sont tels que définis ci-dessus ; ou
(iii) lorsque le noyau C représente un cycle furanne qui peut être substitué par un groupe alkyle comportant de 1 à 4 atomes de carbone, on fait réagir un composé de formule (XVIII) :

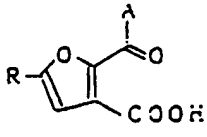


(XVIII)

dans laquelle R représente un groupe alkyle comportant de 1 à 4 atomes de carbone, avec un composé de formule (XIX) :

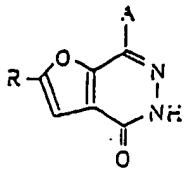
A-COR' (XIX),

dans laquelle A est tel que défini ci-dessus, et R' représente un atome d'halogène, un groupe alkoxy, un groupe aryloxy, un groupe imidazolyle ou un groupe cyano, pour produire un composé de formule (XX) :



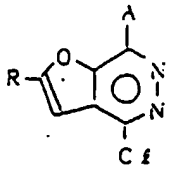
(XX)

dans laquelle R et A sont tels que définis ci-dessus,
on fait réagir le composé (XX) avec de l'hydrazine ou de l'hydrate d'hydrazine, pour produire un composé de formule (XXI) :



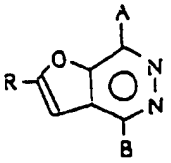
(XXI)

dans laquelle R et A sont tels que définis ci-dessus,
on fait réagir le composé (XXI) avec un agent chlorant pour produire un composé de formule (XXII) :



(XXII)

dans laquelle A et R sont tels que définis ci-dessus, et
on fait réagir le composé (XXII) avec un composé de formule B-H, dans laquelle B est tel que défini ci-dessus, pour produire un composé de formule (I-c) :



(I - c)

dans laquelle A, B et R sont tels que définis ci-dessus.